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HISTORY AS THE BASIS OF MEDICAL EDUCATION.[1]

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Edinburgh.

THERE is much talk today of the "basic sciences" as the foundation of medical knowledge, but the greatest need of medicine, or rather of medical education, today is some common ground upon which all the various sciences may meet, some point upon which they all impinge, and from which they have all originated, some mutual interest in which they may all share.

History, and history alone, can provide such a meeting place. That may appear to you to be a bold assertion, although one must assume, from your presence here today, that you recognize the value of history. Nevertheless, the subject is so full of misconceptions and misunderstandings that some introductory explanation is required, even in such a brief course of lectures.

The historical approach to medicine is not greatly favoured today, although the most logical introduction to any branch of knowledge is a study of its history. Those who teach the fine arts, philosophy, music, economics, to mention a few examples, invariably commence with an explanation of the means by which the present knowledge has been reached; in other words, with an account of the history of the subject. Why not apply this method in the teaching of medicine?

To this question you may answer that medicine, like science, has advanced so rapidly during recent years that it has become changed almost beyond recognition. The student of, say, sculpture may be greatly assisted by a close acquaintance with the statuary of ancient Greece. But of what value to the medical student are, say, the Aphorisms of Hippocrates?

It may be true that as a substitute for modern knowledge Hippocratic learning is of very little use, but as a basis and foundation to present-day medicine it is of incalculable value. Let me elaborate this suggestion by an inquiry into our present attitude towards the history of medicine. There are three distinct views of the matter, three answers to the question, "Why study the history of medicine?".

Strangely enough, there are a few who allege that medicine owes nothing to the past. They share with the late Mr. Henry Ford the view that "history is bunk". Yet those so-called practical people, who wish to discount the past and to concentrate upon what they regard as the latest knowledge, are unwittingly using the material which has been provided by past generations of workers. They may turn a blind eye to the foundation of modern learning, but it is there all the same, because, as Auguste Comte has said, "the older the world grows, the more the living are indebted to the dead".

A second answer to our question is much more prevalent. It is the view of those who find in history, and especially in the history of medicine, something curious, interesting and even amusing—a sugar-coating to the bitter pill of hard medical study, a solace from all the tests and reactions which strain the memory so sorely. For example, a medical writer may commence his description of recent work by comparing with it some obsolete practice of a

[1] Read at a combined meeting of the Section of Medicine and the Section of Medical Literature and History, Australasian Medical Congress (British Medical Association), Seventh Session, Brisbane, May-June, 1950.

century or more ago. Perhaps the worst offenders are the manufacturing chemists, who dig out from the medical literature of early times all sorts of absurdities in order to draw the attention of the reader towards the superior modernity of their own advertised drug. This superficial and flippant attitude towards the history of medicine is unfortunately encouraged by writers, both medical and non-medical, who strive after effect and sensation with but little regard for accuracy.

The third reason for studying the history of medicine is the only sensible view, a view which is steadily gaining acceptance. Medical men desire to study history because the historical approach provides for medicine a sound cultural basis; without it, medicine becomes a mere technical accomplishment. Some such antidote to the technicality of medicine is greatly to be desired. Many have deplored the modern tendency of medicine to become a technique, or at best a handicraft, comparable to veterinary medicine and lacking that humanism which was so prominent a feature in past ages, even until last century. Universities are now fast becoming technical schools instead of cultural centres. Medicine has become medical science.

Science has captured the popular imagination. Science itself has become highly revered and almost deified, so that the word "scientific" is a synonym for true, accurate and correct, and if we wish to disparage a method or a discovery we call it "unscientific". It would even appear that knowledge has outdistanced wisdom, and that the scientific machine has become too great for mankind to control. Of course, it would be absurd to attempt to stem the flood-tide of science, so full of promise and so helpful to humanity when rightly used. Nevertheless, medicine must not be allowed to become a mere technical accomplishment or a handicraft. Universities must be centres of culture, and not simply technical schools. The power and precision of science need not outweigh all other aspects of medicine. It has been all too clearly demonstrated that science ought not always to have the last word.

So far as medicine is concerned, there is another reason why science is so highly regarded at the expense of art, and that is man's inherent love of novelty, his tendency to regard the latest treatment as the best treatment, his desire for all new things. It is sometimes forgotten that this praise of the new was Shakespeare's "one touch of nature":

> For Time is like a fashionable host
> That slightly shakes his parting guest by the hand,
> And with his arms outstretch'd, as he would fly,
> Grasps in the comer: Welcome ever smiles,
> And Farewell goes out sighing.

Novelty, however attractive, is not always excellent, and even science cannot unlock every door into the unknown. The worship of novelty has influenced the progress of medicine for centuries; we are still too prone to imagine that we do things far better than our forefathers.

The humanistic aspect of medicine, and all that constitutes "The Art", has been swallowed up in this flood of science, while medicine tends to become "impersonal", indeed almost "inhuman".

Science, especially medical science, has progressed so rapidly that the sense of proportion has been lost. The mass of factual knowledge has become embarrassing. We are unable to use it, and sometimes we could almost wish that further progress could be halted, so that we might draw breath and make a satisfactory use of what we already possess. Many of our leading scientists today view with concern the fragmentation of knowledge called specialism, which is more to be deplored in medicine than in science, since medicine must ever be an art as well as a science. There is great need for a stocktaking of the present situation, great need for each special branch of medicine to consider how its collection of knowledge may be linked up with the knowledge in other fields. "Integration" is the word which best expresses this ideal. But how is integration to be achieved? A sounder knowledge of what are known as the basic sciences has been suggested as the answer. It seems advisable, however, to include the basic arts, especially logic and philosophy, as well as the sciences. The medical school of Salerno, as long ago as the eleventh century, decreed that the study of medicine should be preceded by a three years' course of logic. And many centuries later, William Cullen commenced his lectures on medicine in the University of Edinburgh by telling students that he "would strive to make them philosophers as well as physicians". The gulf between medicine and the humanities is far too wide, and it is steadily becoming wider, owing to the increase of specialized knowledge.

History, if properly used and suitably taught, can solve this problem by bridging the gap. History, the basis of all knowledge, supplies the key to the present and the future. But it must not be presented as a collection of facts, or it then becomes simply another specialty. It must rather provide a meeting-place for all the various branches of medicine, for the sciences bearing upon medicine, and even for the humanities—the classics, literature, philosophy in the wide sense, archæology, fine art, all of which have exercised an influence upon medical progress in the past, a beneficial influence which would still continue if medicine would only be less self-satisfied and more ready to cultivate the non-medical muses.

Medicine is surely the most intimately humanistic of all the humanities; it can never be wholly a science. How right was Sir Thomas Browne when he wrote: "There are many things true which are neither inducible by reason nor confirmable by sense."

Another great trend or tendency of modern medicine is expressed by the word socialization. We hear a great deal today about social medicine, as if this was a new subject and a new idea. It is at least as old as Hippocrates, who about 400 B.C. wrote an interesting little book on airs, waters and places, showing how man reacted to his environment and how various diseases were prevalent at various ages and during various seasons of the year.

The study of the health of mankind in the mass also attracted the Arabian physician Avicenna, who discussed in his canon of medicine, about A.D. 400, such matters as water supply and housing in relation to health.

It is generally believed that the first to insist upon the need for public health legislation was Johann Peter Frank, of Vienna, who made it his mission in life to awaken a health conscience, not only in the people but in their rulers. Strangely enough, this idea of preventive medicine was fostered in this country not so much by medical men as by a philosopher, Jeremy Bentham (the bicentenary of whose birth was celebrated this year), and by a lawyer, Sir Edwin Chadwick, who constantly advocated what he called "the sanitary idea".

The application of the statistical method in medicine, which is proving so valuable in public health today, owed much of its origin to the work of the Belgian, Adolphe Quetelet (1796-1874), who is rarely mentioned in histories of medicine. Quetelet was an early pioneer of mass observation.

Of course, preventive medicine has gone a long way since then, and legislation has accomplished much. Nevertheless, we would do well to recall the remark of Plato: "It may be a great evil that physicians kill their patients or that captains lose their ships, but it would be a greater evil if each detail in the practice of medicine or of seamanship were regulated by law." No, there is something more in medicine than mass regulation based upon statistics, or exact technical treatment based upon the latest scientific test. And what that something is, history alone can show. Only by the historical approach can we explain that factor which constitutes the art of medicine, and which is quite as important in practice as the science of medicine.

And now, having indicated the scope and meaning of history as applied to medicine, and having tried to show how valuable it may prove as the foundation of all medical knowledge, let us proceed to discover the best method of study. The historian's task consists of analysis and synthesis. First he collects his information, then he chooses certain facts, he arranges them in order, he discusses their relative value, and he presents them to the reader or listener. He must not be merely an artist in scissors and paste. That part of his task, the collection, is easy. Selection is more difficult, while presentation is the hardest task of all. The historian must introduce enough bio-

graphy to give reality to his characters, but he must avoid the tendency to dramatize, a tendency which has been greatly favoured in America during recent years.

Two definite rules must guide the medical historian: he must preserve an accurate sense of time, and he must relate medical progress to environment. A clear chronology is essential. We must know, at least roughly, when certain things happened and when certain men lived, although there is no need to burden one's memory with dates, which, after all, are only the signposts of history.

Just as we can explore medical history in time, we can also explore it in space. From Greece and Rome medicine passed to the Moslem world, and entered or reentered Europe by the gateway of Salerno; thence it went to Montpellier and Padua, to Paris and Leyden, and eventually to Edinburgh and Philadelphia. The geography of history is regarded as of sufficient importance to justify the inclusion of a map in histories of medicine.

Every student should know something of the history of his own medical school. Local medical history is a source of great interest and stimulus. The medical student ought to be familiar with the heritage of which he is the heir. Someone ought to write a history of the medical schools and hospitals of Australia and New Zealand. So far as I am aware, this has not yet been done and it is well worth doing. And as for the history of medicine and of medical practice generally in Australia, what a noble and worthy theme that would afford. Of course, there are men like Robert Scot Skirving, of Sydney, and W. L. Crowther, of Hobart, who have delighted and instructed us with their accounts of the pioneers, but what a magnificent story could be told as a full-length narrative and what a valuable incentive it would be to student or practitioner alike. Interested members of this Section would find here a most fruitful field for historical research.

All over the world there is a growing interest in the history of medicine, the result, perhaps, of a desire to escape from the bonds of technicality, and to reinfuse the humanistic ideal into the art of medicine.

Many other sources are available. The history of medicine is indeed a many-sided subject. Before the invention of printing, history was recorded in manuscripts, and even before the invention of writing, the story of man may be read from buildings and cave drawings, from mummies and skeletal remains, from tools and instruments. Even in recent times we may learn much medical history from the study of postage stamps (and medical philately is an attractive hobby), or from medals, and even from monuments and tombstones.

A history of medicine may be divided into a description of various branches—anatomy, surgery, pathology, obstetrics and so on; or it may be a history of diseases. Syphilis, for instance, has a much debated history, and so has tuberculosis. The history of epidemics provides many lessons. No student of epidemiology can afford to be ignorant of the effect of the Plague of Justinian, or of the Black Death, or of the means by which Edward Jenner arrived at his discovery of vaccination.

As for the history of instruments, it is of interest to the student of medicine to know the curious history of obstetric forceps and the story of the invention of the stethoscope.

Of course, the men who have made medical history are in themselves attractive subjects of study. History is indeed a series of biographies, and the biographical method provides an attractive viewpoint. Who has not been thrilled by the life story of Eve Curie, of Pasteur, of Lister, of Paget, of Osler, of John Hunter, to mention only a few of the immortals?

The medical classics form another means of approaching this fascinating subject. Some of them are not easily found. The first editions of Auenbrugger on percussion (the "*Inventum novum*", as it is called), Edward Jenner's "Inquiry", Harvey's "*De motu cordis*", Withering's "Account of the Foxglove", are all very rare, but most of them have been reprinted and all are worth reading. It is well worth while to read the "Aphorisms" of Hippocrates, the work of Ambroise Paré, Laennec's great work on auscultation, Richard Bright's case reports, and Lister's description of the first application of his antiseptic method. Those classic descriptions ought to be better known, and most of them are clear and delightful to read, which cannot be said of much of the medical literature of today.

Perhaps the most interesting of all aspects of the history of medicine is that which deals, not with bare facts regarding the pioneers and their discoveries, but with the fashions and trends and systems—the ways of thought—which have influenced medicine since the earliest times.

The history of ideas is of all histories the most subtle, and perhaps the most important. For centuries medicine was dominated by magic; then came the doctrine of the humours, which was the basis of medical practice for many more centuries. The mechanical and chemical schools and their day, the iatro-physicists and iatro-chemists of the seventeenth century. But it soon became obvious that such "systems", to use the words of Claude Bernard, "did not exist in nature, but only in men's minds". Moreover, medicine was not an exact science, but, like navigation and agriculture, was subject to conditions which man was powerless to control.

Nevertheless, the fashions and trends of medicine remain. Today we witness the epoch of the specialist, tomorrow we may find the specialties reuniting under some dominating influence. So it goes on. The science changes, but the art remains constant. And in the long run, it is the art that matters.

I have tried to show you why the history of medicine is important as the basis of all medical study and as a means of counteracting the specialist tendency. I have attempted to sketch the various routes by which one may approach the subject with advantage. In conclusion, let me offer some remarks on the method of teaching which ought to be adopted.

Every university and medical school ought to have a place in its curriculum for the history of medicine, not as a compulsory subject nor yet as an exhaustive and complete course of lectures, but rather as a series of lectures giving the main outlines and stimulating the student to continue the study for himself. Furthermore, the courses of instruction in surgery, medicine, obstetrics, and so on, ought each to have at least one lecture devoted to the history of the subject.

Everyone recognizes today that the world is in a sorry state. But no one seems to have realized the power of medicine as a factor in the reconstruction towards which we all strive. Medicine, at once scientific and humanistic, may hold the key to the integration and unification of knowledge, which is the first step towards a harmonious advance. Yet without history the effort is vain, because history, as Trevelyan so clearly states, "is the cement which holds together all the studies relating to the nature and achievements of man". The history of medicine ought to be the foundation and background of all the varied studies at present embodied in the medical course. The need for such a basis was never greater than it is today.

The medical man can never be a completely detached observer or onlooker. He himself is human and subject to the same frailties and troubles as his patients. Only by the study of history can the medical student secure the comprehensive view which, if not essential for degree examinations, is certainly needful if he is to acquit himself under cross-examination by his patients. This extra study need impose no great strain upon the student who is already heavily burdened with learning. It is a fascinating relaxation for spare moments, a recreation rather than a task.

I have given you the merest outline of what is meant by the historical foundations of medicine. Nothing has been said of the amazing developments of recent years in the prevention and treatment of disease and in the social implications of national health. Today there is a widespread need for a return to the simple observational methods of Hippocrates and a more liberal infusion of the humanities into medical education. History, philosophy, literature, music—all have their influence upon medicine. Medicine is more than a means of livelihood or occupation; it is a vocation, a profession, an art.

SOME ASPECTS OF FAT METABOLISM.[1]

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THE series of lectures of which this paper forms a summary was designed to present in a comprehensive manner the development of modern concepts of fat oxidation in the liver. Much of this has appeared in a number of excellent reviews over the past few years, so that this communication has been condensed to present only those aspects which are of direct importance to the development of a working hypothesis to account for biochemical changes observed in the fatty liver.

The initiation of the first hypothesis, developed by Knoop (1904) to account for the oxidation of phenyl-substituted fatty acids, has led, over a period of years, to several theories. The original hypothesis suggested that β-oxidation of fatty acids occurred with the splitting off of two carbon atoms at a time until a four-carbon acid remained. Oxidation at the β-carbon of this acid then resulted in the formation of acetoacetic acid. In other words, one mole of acetoacetic acid was formed from one mole of fatty acid. With the advent of improved techniques it became clear that more than one mole of acetoacetate was produced per mole of fatty acid, and as a consequence the theory of multiple-alternate oxidation originally proposed by Hurtley (1916) was suggested by Jowett and Quastel (1935). It was envisaged that oxidation occurred simultaneously at alternate carbon atoms along the fatty acid chain and that cleavage then occurred at every fourth carbon atom. Thus a molecule of 16 carbon atoms would produce not one but four molecules of acetoacetate. This hypothesis was accepted in spite of the fact that it could not explain certain phenomena, for example, the formation of acetoacetate from acetate and from the lower members of the fatty acid series containing odd numbers of carbon atoms. Attention was later refocused on the original Knoop theory; β-oxidation was a phenomenon about which there was no doubt, and, moreover, it was certain that 2-C fragments were split from the fatty acids—at least from the lower members of the series. It occurred to MacKay and co-workers (1940) that the formation of ketones from the odd carbon atoms could best be explained on the assumption that the 2-C fragments reunited after having been split from the fatty acid chain. This theory of β-oxidation and condensation lacked experimental support until Weinhouse, Medes and Floyd (1945) were able to prove it conclusively by the use of C^{13} labelled octonoate.

The 2-C unit thus appears to be the central figure in the catabolism of the fatty acids. This is also true of the anabolic side, since Stetten and Schoenheimer (1940) were able to show that palmitic acid with 16 carbons was converted to stearic acid with 18 carbons. Furthermore, it has been shown by Rittenberg and Bloch (1944) that labelled acetate is incorporated into fatty acids. The nature of this 2-C fragment is a question which has vexed biochemists for some time and one which is still unanswered. A short discussion of the possibilities which have been considered is perhaps best left until we consider very briefly some of the finer points of the machinery by which the degradative changes in the fatty acids are brought about. It is always the goal of the biochemist to find the nature of the enzymes concerned in a particular transformation, and since the liver is the chief, if not the only, site of the formation of acetoacetate, this organ is clearly the one to be investigated.

Progress in carbohydrate metabolism was greatly accelerated by the use of breis and homogenates, and it was logical to apply such techniques to this problem. However, once the integrity of the liver was destroyed to form a brei or homogenate, the oxygen consumption fell to very low levels, and the capacity to oxidize added fatty acid substrate actually fell to zero. This behaviour of the liver provided a most formidable barrier to those engaged in the study of the oxidation of the fatty acids.

Munoz and Leloir (1943) were first to achieve partial success, although their homogenates lost their activity in a short time. In spite of this drawback they were able to show that adenylic acid, phosphate, fumarate, cytochrome *c* and oxygen were necessary for fatty acid oxidation. Interpretation of these results was made possible by the work of Lehninger (1944), from which it became clear that adenosine triphosphate (ATP) was an essential component of the system. This, then, allowed of an explanation of two main points: (*a*) why it was so difficult to prepare homogenates with activity, and (*b*) why Munoz and Leloir found adenylic acid, fumarate, oxygen, phosphate and cytochrome *c* essential to the system.

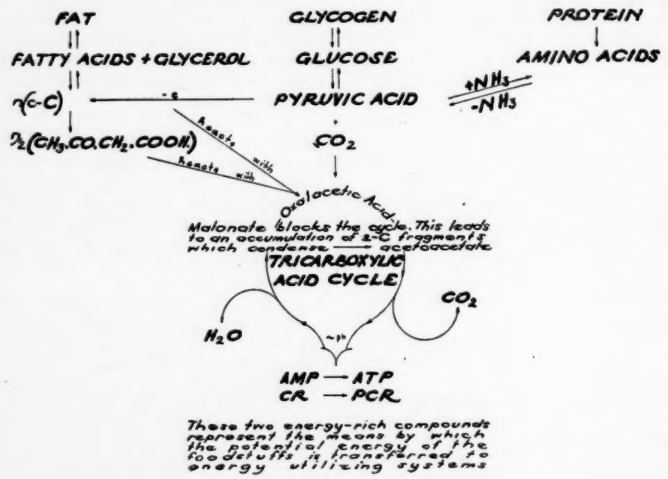

FIGURE I.

In the body ATP is a very labile substance and is partially, but rapidly, dephosphorylated once the integrity of the cell is damaged. Thus, the preparation of an homogenate would lead to the dephosphorylation of a large part of the ATP. In addition, there is the effect of dilution which would further reduce the concentration of ATP. As far as point (*b*) is concerned, it is known that fumarate oxidation is coupled with the esterification of inorganic phosphate and that for such oxidations oxygen and the cytochrome system are necessary. In an intact system oxidation of fumarate would give rise to ATP by phosphorylation of the added adenylic acid, and the ATP would then play its role in the oxidation of the fatty acids. The finding that ATP is an essential part of the mechanism by which fatty acids are degraded has led Lehninger (1945) to suggest that a phosphorylation of the fatty acid is one of the initial reactions. The suggestion that acetyl phosphates are likely to be produced gives a clue to the possible nature of the 2-C fragment referred to earlier. It is clearly of some considerable importance to determine the actual identity of this fragment, and it has been suggested that it is identical with acetyl phosphate, the occurrence of which in a biological system was first announced by Lipmann (1940). It is not the purpose of this summary to detail the extraordinarily interesting and fundamental work that has gone into this problem, which is still unsolved. Irrespective of its nature there

[1] This article contains the subject matter of a series of special lectures given at the University of Queensland in May, 1949.

can be no doubt as to its existence, and it is envisaged that in the breakdown of carbohydrates, fats, or proteins this compound will ultimately appear. It has long been realized that there must be some close association between these dietary constituents, and the 2-C compound provides this association at an intermediary level (Figure I).

At this point may be mentioned the direct association of the tricarboxylic acid cycle, with the final breakdown of a fatty acid to carbon dioxide and water, since it is relevant to arguments to be developed later. Realization of the possibilities of such a reaction arose from the work of Jowett and Quastel (1935*a*), which showed that the addition of sodium malonate to respiring liver slices resulted in the appearance of increased amounts of acetoacetate. Since malonate is an inhibitor of succinoxidase, it was later thought that the acetoacetate arose by virtue of the blocking by malonate of the normal channel by which complete oxidation occurred. Such a blockage would then permit the condensation of the 2-C fragments with the appearance of acetoacetate.

The first evidence of an actual mechanism came from the work of Rosenthal and Wieland (1943) and later from that of Breusch (1943, 1944). Briefly, it was found that there was an aerobic formation of citrate from acetoacetate and oxalacetate. The enzyme was called citrogenase and was found in large amounts in heart muscle and kidney tissue, but little, if any, was present in liver tissue. Since this pioneer work, much has been done on the problem, and it is now abundantly clear that the tricarboxylic acid cycle provides a pathway for the complete oxidation of fatty acids.

In the intact animal the liver is the chief site for the metabolism of the fatty acids, and thus the metabolic behaviour of the fatty liver is of some interest. Some time ago we became interested in the respiratory behaviour of such livers as a result of a publication (Meier and Thoenes, 1933) which indicated that the livers from guinea-pigs poisoned with phosphorus and chloroform had oxygen consumptions at least 50% greater than normal. Closer investigation of this effect seemed worthwhile, particularly as previous workers had expressed oxygen consumption figures on the basis of wet weight. This method of calculation is clearly open to serious criticism, since the fat content of liver may vary from about 5% to as high as 30%. It proved possible to confirm and, to some extent, extend the work of Meier and Thoenes, and some of the results are given below.

It is clear (Table I) that the livers from those animals poisoned with carbon tetrachloride are respiring at a considerably greater rate than normal, and that in general the magnitude of the increase over the normal value runs parallel with the fat content. Since the amounts of acetoacetate produced are also much increased over the normal, it may be inferred that this increase and the increased oxygen consumption occur as a result of increased oxidation of fatty substrate. Similar results have been found in the case of other types of fatty livers which have been investigated; that is, those arising from phosphorus poisoning and injections of extracts of the anterior lobe of the pituitary gland (Ennor, 1941).

In an extension of the work on fatty livers, Ennor and Stocken (1948) were able to show that livers from guinea-pigs poisoned with carbon tetrachloride contained increased amounts of ATP and phosphocreatine. Experimentally, therefore, the following facts emerge: in the fatty liver arising from injections of carbon tetrachloride there is (*a*) an increased oxygen consumption; (*b*) an increased acetoacetate production; (*c*) an increased level of energy-rich phosphate bond (~ph after the Lipmann (1941) terminology) as represented by the adenosine polyphosphates and phosphocreatine.

In the light of our present knowledge of fat metabolism these findings may be interpreted and a picture drawn of the events which take place in a liver following the deposition of fat. The picture applies to the type of fatty liver which has been reasonably fully investigated—that produced by the administration of carbon tetrachloride. It is not possible to predict what will happen in other types of fatty liver, but until the contrary is proven by experimentation it would seem reasonable to expect them to behave similarly.

The series of events then is that fat accumulates, and, since the fat content may rise from about 5% to as high as 30%, an extensive enzymic rearrangement must be produced within the liver cell. The fat must be removed in some way, and oxidation is at least one mechanism employed, as is indicated by the increases in oxygen consumption and acetoacetate production. The tricarboxylic acid cycle, as we have seen, provides a pathway for the complete oxidation of fatty acid residues and at the same time provides an important means for the synthesis of ~ ph. It is therefore logical to assume that the increased levels of ~ ph which have been found have their origin in the passage of fatty acid fragments through this cycle. The events which have been described are illustrated graphically in Figure I.

TABLE I.

Oxygen Consumption and Acetoacetate Production in Livers from Normal and Carbon Tetrachloride Poisoned Guinea-pigs. No Substrate Added. Results taken from work of Ennor (1942).

Normal.			Carbon Tetrachloride Poisoned.		
Fat. (Grammes *per Centum.*)	Qo_2.[1]	Qac.[1]	Fat. (Grammes *per Centum.*)	Qo_2.	Qac.
6·8	6·2	0·3	11·5	8·3	0·8
6·9	8·4	0	12·4	10·9	0·9
5·4	7·6	0·2	10·7	11·2	0·6
6·5	6·7	0·2	15·0	13·9	1·2
5·3	6·4	0·1	19·2	15·5	1·1
Mean : 6·2	7·1	0·2	13·8	12·0	0·9

[1] Qo_2 is defined as the number of cubic millimetres of oxygen consumed per milligramme of dry, fat-free tissue per hour, and Qac as the number of cubic millimetres of carbon dioxide equivalent to acetoacetic acid produced per milligramme of dry, fat-free tissue per hour.

The appearance of phosphocreatine in large amounts —up to 15 milligrammes *per centum* (Ennor, 1949)—in the liver is surprising, particularly as one can scarcely ascribe a function in this organ analogous to that given the compound in, for example, voluntary muscle. In this latter tissue, the demands for sudden periods of work are great and, according to the modern theories, are met by the breakdown of ATP with the formation of adenosine diphosphate (ADP). One restoration mechanism lies in the transference of ~ ph from the large reservoir of phosphocreatine to ADP with the reconstitution of ATP. In the liver, however, there is no such sudden demand for energy and the fact that accumulations of phosphocreatine do occur suggests that this compound may act as a reservoir of ~ ph which is available to cellular reactions without the necessity of prior passage through the adenylic acid system.

More surprising perhaps is the finding that such comparatively large amounts of ~ ph do actually accumulate in the liver. A search of the literature has not revealed one instance where an absolute increase in ~ ph occurs as a result of increased oxidation of a substrate. In fact, such a result would not be expected, and an explanation of this finding must await the result of investigations now in progress. Clearly much information will be gained on the state (dynamic or otherwise) of this energy "pool" by the use of radioactive isotopes, and this work is scheduled for early commencement. In the absence of experimental verification the most reasonable explanation, if we assume no alteration in the adenosine triphosphatase content of the liver, is the assumption of a blockage of one or more of the paths by which ~ ph is normally made available to endergonic processes. Such an effect would lead to an accumulation of ~ ph as a result of a "damming-up" process.

Recent work in the United States indicates that protein synthesis involves ~ ph, and it is possible that protein synthesis is substantially reduced in degree in such livers as have been considered. In fact on this assumption an

explanation can be attempted for the peculiar and rapid influx of fat into the liver following the injection of many hepatotoxic substances. This explanation involves a concept which was introduced by Gavrilescu and Peters (1931) and which was aptly termed a "biochemical lesion". The pathologist is able to demonstrate, even in the early stages of carbon tetrachloride poisoning, changes in the microscopic structure of the liver. These changes are the end, or near end, result of a biochemical lesion the initial effects of which can be envisaged as some, as yet undefined, change in the ultramicroscopic structure of the hepatic cell—a change in the enzyme relationship within the cell. The correction of this very early change must place an energy load on the synthetic resources of the cell—a load which cannot be met from the normal substrate resources actually present within the cellular boundaries. From the viewpoint of thermodynamic efficiency fat is the substrate best suited as an energy source. Under the influence of, as yet, unknown factors, fat is transferred from the body depots to the liver, and this extra substrate is then oxidized through the tricarboxylic acid cycle. The energy so produced is funnelled off and bound in the form of ~ ph. Now the fact that microscopic changes are visible in the cellular structure implies that the repair processes cannot keep pace with the destructive processes; that is, with the speed with which the biochemical lesion spreads. It is possible that the rate of protein synthesis, and other energy-demanding reactions, may be substantially reduced, and that this may be an early effect of carbon tetrachloride. Under these circumstances, then, and in spite of the fact that readily available energy is now being generated, it cannot be utilized and an accumulation results. If this concept be correct, the accumulation of liver fat which occurs after the administration of many toxic substances is not, in itself, a pathological process but one which is merely a reflection of the demand for energy necessary for the repair of the biochemical lesion.

In conclusion, it must be pointed out that there is at present but little experimental support for the hypotheses put forward. It is hoped that work now in progress will shed some light on this problem, which has so much of interest from the viewpoint both of the laboratory worker and of the clinician. Irrespective of the correctness of the hypotheses, it would seem certain that the ultimate solution of the problems discussed lies in the hands of the biochemist, for, as Peters (1948) has remarked, "therapy will be most effective when the biochemical lesion is understood and reversed before it has gone too far".

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ERRORS INVOLVED IN THE COUNTING OF BLOOD CELLS.

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IT is now forty years since "Student" (1907) drew attention to an important source of error in the use of the hæmocytometer: the error of random sampling, which arises from the fact that the cells are not distributed uniformly over the floor of the counting chamber. The practical importance of his work has never been fully appreciated, and the result is that many people grossly over-estimate the accuracy of blood counting. For example, Berkson, Magath and Hurn (1940) have examined the criteria which certain text-books lay down for "permissible" discrepancies in duplicate counts, and it is quite clear that the margin of error usually allowed is far too small. Again, various observers have noted fluctuations in the level of leucocytes and have considered that these were physiological diurnal variations; but subsequent work by Ponder *et alii* (1932) showed that they were due in part to errors of counting. It seems possible that a mistake of a similar kind has been made by Davis (1946), who stated that the feeding of choline to dogs produced a hyperchromic anæmia that responded to the administration of folic acid. At any rate, the changes he observed in the erythrocyte count were probably no greater than the errors of measurement. This interpretation is supported by the fact that other workers have failed to confirm his findings.

Because of the frequency with which blood counting is used both for research and for routine clinical investigation, it seems worth while to review the errors involved. It is necessary to consider separately the errors that arise in the making of a differential count and those that occur during the use of a hæmocytometer.

ERRORS MADE DURING THE USE OF A HÆMOCYTOMETER.

These errors may be listed as follows: (i) The drop of blood may be diluted with tissue fluid or may be otherwise unrepresentative of capillary blood. (ii) The correct amount of blood or diluting fluid may not be taken into the

pipette, either because the worker is careless or because the pipette is inaccurate. (iii) The correct amount of diluted blood may not be placed in the counting chamber if the latter is inadequately calibrated. (iv) Mistakes may be made in the counting of the cells. (v) The small population of cells counted may not be representative of the blood that is being examined—in other words, there is a sampling error.

The last type of error listed is in a category by itself. In the case of the others the investigator may greatly reduce the size of the error by increasing his carefulness and skill and by using good, calibrated apparatus; but carefulness on the part of the worker is not, in general, important as far as sampling errors are concerned. It is true that, as a result of negligence, gross sampling errors may occur at times; for example, a count may be carried out on a specimen in which the leucocytes have clumped together into large aggregates. But it is also true, and very important, that a sampling error occurs even if the observer works with perfect technique and has had a wide experience in hæmatology. This error arises from the irregular distribution of the cells, and its size depends on the total number of cells counted. One of the main purposes of this article is to remind readers of the existence and extent of this error, and it will therefore be discussed first.

Sampling Errors.

In the course of carrying out an erythrocyte count, one determines the average number of red blood cells per small square. How reliable is this average? If the count was repeated on the same sample of blood, how well would the results agree? In other words, what is the standard error of this mean value?

Suppose that an erythrocyte count is carried out in the usual way; that is, blood is diluted to one part in 200 and the red blood cells overlying 80 small squares of the grid are counted. Now, since the cells fall at random on these 80 squares, the probability that a given cell will fall on a given square is 1/80, and the probability that it will not fall on that square is 79/80. But if the probability that an event will occur is p, and the probability that it will not occur is q, and the number of trials is n, then the standard deviation of the distribution of the number of occurrences is given by the formula $\sqrt{pqn}$. For example, the number of red blood cells overlying the small squares may be 8, 10, 3, 4, 2, 8, and so on, there being 80 values. These values constitute a distribution, and the standard deviation of this distribution is, according to the formula $\sqrt{\frac{1}{80}\,\frac{79}{80}\,\frac{n}{1}}$ where n is the total number of cells counted.

Now the standard deviation of the mean of a series of values (or standard error of the mean, as it is usually called) is obtained by dividing the standard deviation of the series, as given above, by the square root of the number of cases on which the mean is based. In the above example the mean value per square is based on the values obtained from 80 squares. Hence the standard error of this mean value is $\sqrt{\frac{79n}{80\times 80\times 80}}$. This is approximately $\frac{\sqrt{n}}{80}$. The total number of red blood cells counted is 80 times the mean number per square, and the standard error of the total number counted is also 80 times the standard error of the mean number per square. That is, if the total number of cells counted is n, the standard error of the total number of cells counted is $\sqrt{n}$. For example, if there are 625 erythrocytes in the volume of blood counted ($\frac{1}{10000}$ cubic millimetre), the standard error of the count is 25 erythrocytes. Now in any large-scale series of counts on samples chosen at random from blood containing 625 erythrocytes in $\frac{1}{10000}$ cubic millimetre, one would expect to obtain an average result of 625 erythrocytes, if the technique of counting was perfect; but one would also anticipate sampling errors in the individual counts. Assuming that the counts are normally distributed, one would expect that, in five counts out of 100, the sampling error would be at least 1·96 times the standard error—that is, at least 49 erythrocytes. In one count out of every 100 one would expect the sampling error to be 2·58 times the standard error—that is, 64 erythrocytes. These results may be expressed by the following statements: (*a*) If the true count is 6·25 million erythrocytes per cubic millimetre, the probability of obtaining a count greater than 6·74 (that is, 6·25 + 0·49) or less than 5·76 (that is, 6·25 − 0·49), as a result of random sampling alone, is 0·05. (*b*) If the true count is 6·25 million erythrocytes per cubic millimetre, the probability of getting a count greater than 6·89 (that is, 6·5 + 0·64) or less than 5·61 (that is, 6·25 − 0·64), as a result of random sampling alone, is 0·01.

It must be emphasized again that the above-mentioned errors are minimal, since they do not allow for inaccuracy on the part of the laboratory worker; but it has been shown that when errors of technique are ruled out, there is good agreement between the actual counts and the counts predicted by the above theory. However, "Student" himself pointed out that in using this theory one supposes that a particle has the same chance of falling on an area already containing several particles as it has of falling on an area altogether unoccupied. If the number of particles is large, this assumption will not be true and the actual distribution will show a slight departure from the theoretical distribution owing to what Berkson, Magath and Hurn (1940) have tentatively described as an "overcrowding" effect. It is interesting that these authors obtain such an effect in counting red blood cells, but not in counting the much less numerous white blood cells.

Other Errors.

With the slight reservation mentioned about "overcrowding", then, the theory given above explains the bulk of such errors in hæmocytometer counts as are obtained in careful research. However, in most cases additional errors have to be considered. These have been listed earlier and two of them may be dismissed very briefly. (i) As for errors in enumerating the cells, it is sufficient to note that mistakes can readily be made in this process but that a careful observer can eliminate them by working objectively and methodically. (ii) It is generally agreed that errors are introduced if blood is squeezed from the puncture wound rather than allowed to flow freely.

More detailed consideration has been given by Berkson and co-workers to errors in the calibration and use of the pipette and counting chamber. There is a certain artificiality about the calculation of such errors, for, obviously, the apparatus may vary widely in accuracy and the workers in skill. It is nevertheless interesting to see what errors over and above the basic sampling error were introduced when experienced workers used "satisfactory" apparatus. They tried ten pipettes and ten counting chambers, all of which had been passed as satisfactory by the United States Bureau of Standards. This perhaps approximates to the condition found in a good laboratory where a blood count may be made with one of several hæmocytometers, but where none of the pieces of apparatus is grossly defective. The figures to be given are obviously inapplicable if one is using apparatus inferior to that employed by Berkson *et alii*.

The errors introduced by the act of pipetting were almost the same as those caused by the use of the counting chamber. For our present purposes it is convenient to express the errors of pipetting in terms of the variance which they introduced into the results of blood counting. The variance is, of course, the square of the standard deviation; but, as will be seen later, it is more convenient than the standard deviation for one of the most important of our calculations.

It was found that the variance introduced by the use of a variety of pipettes was $0{\cdot}002209n^2$, where n was the total number of cells in the specimen counted. It is convenient to call this variance V_p. Similarly, the variance introduced by the use of a variety of counting chambers may be called V_c; it amounted to $0{\cdot}002116n^2$.

The size of these errors is best appreciated by comparison with the error of random sampling, and a comparison of these three main errors will now be made. It will be recalled that the standard deviation due to the last-mentioned error is $\sqrt{n}$ or, if we allow for an "overcrowding" effect in the case of red blood cells, $0{\cdot}92\sqrt{n}$. The variance due to the error of random sampling, which we may call V_s, is therefore n in the case of white blood cells, and $0{\cdot}8464n$ in the case of red blood cells.

Comparison of the Error of Sampling, the Error of Pipetting and the Error of Using the Counting Chamber.

The convenience of expressing the error of sampling, the error of pipetting and the error of using the counting chamber in terms of the variance that they introduce into the result is that the total variance, which we may call V_t, is equal to the sum of the variances due to each of the three components. In symbolic form we may write $V_t = V_s + V_p + V_c$.

Table I shows the variance to be expected as a result of the three main errors, when the erythrocyte count, in millions per cubic millimetre, ranges from 0·5 to 7·0. It will be noted that the error due to random sampling is the greatest of the three only when the total number of cells counted is less than 400. This has an important implication. The standard deviation due to random sampling can be reduced in relative size by the counting of more and more cells. For example, when the number counted is 400, the standard deviation due to random sampling is $\sqrt{400} \times 0{\cdot}92$; when the number of cells counted is 800, the corresponding standard deviation is $\sqrt{2 \times 400} \times 0{\cdot}92$; and, in general, an n-fold increase in the number of cell counted causes only a $\sqrt{n}$-fold increase in the standard deviation due to random sampling. But the position is different as far as the two other errors are concerned. In these two cases the relative standard deviation introduced into the count is the same whatever the size of the count. For example, consider counts of 400 and of 800 cells. In the first case, V_p is $0{\cdot}002209 \times 400^2$, and in the second case it is $0{\cdot}002209 \times 800^2$; that is, it has increased fourfold. The standard deviation, being the square root of the variance, has consequently increased twofold; so that, in doubling the number of cells counted, one has also doubled the standard deviation due to the error of pipetting and that due to the error of using the counting chamber; or, more generally, when one increases the number of cells counted n-fold, one also makes an n-fold increase in the standard deviation due to the two errors mentioned. It is for this reason that these errors, though relatively small in the case of counts of, say, 100 cells, become more important than the error of random sampling when the number of cells counted is increased.

By considering these conclusions one can lay down certain important practical rules for increasing the accuracy of using the hæmocytometer. It has already been seen that one can make the error of random sampling unimportant by counting a sufficiently large number of cells. If one uses the same pipette and same counting chamber throughout, and so, for practical purposes, eliminates variation due to pipetting and to the use of the counting chamber, one can reduce the error of the count merely by increasing the number of cells counted. But, as has already been mentioned, there are many practical situations in which it is impossible to use the same apparatus for a series of blood counts. The best one can hope to do is to use apparatus which is "satisfactory" in the sense already defined. In these cases one has to consider errors due to the use of apparatus as well as the error of random sampling; and the former errors are not decreased by the counting of larger numbers of cells. In such circumstances it is pointless to count too great a number of cells; but the question naturally arises as to what is meant by "too great a number of cells" in this context. If we can take as typical the errors which Berkson and co-workers apportion to the use of apparatus, we can answer this question. A reference to Table I will show that when 500 cells are counted the error due to random sampling is less than that due either to pipetting or to the use of the counting chamber. It would be reasonable to argue, therefore, that there is no point in counting more cells than this; for, in doing so, one would merely reduce what is already the smallest of the three main errors and would not affect the other two. It is worth noting that, when erythrocyte counts are in the region of 5,000,000 per cubic millimetre, one obtains a total count of about 500 cells by counting the cells overlying 80 small squares. If there is an anæmia in which the count has been reduced to 2,500,000 per cubic millimetre, it is necessary, of course, to double the area counted in order to find 500 cells.

So far no method has been given for reducing the error of pipetting or of using the counting chamber. These errors can be reduced by repeating the estimation with a second pipette and a second counting chamber and then averaging the results. The variance of the distribution of the mean of n observations is equal to the variance of the distribution of a single observation divided by n. Hence if two counts are performed instead of one, the variance is thereby halved. We may consider by way of illustration the case in which an initial count of 500 cells has been made, so that, according to Table I, the total variance is 1504, which means that the standard deviation is approximately 39. Consider the relative merits of (*a*) increasing the number of cells counted to 1000, and (*b*) repeating the count with a second pipette and a second counting chamber. In the first case the new total variance, as shown in Table I, will be equal to 5171; that is, the standard deviation will be 72. In the second case the variance will be $846 + \frac{1}{2}(2209 + 2116)$, that is, 3008; so that the new standard deviation is 55. In summary, then, the original standard deviation was 39 when the count was 500, which is equivalent to a standard deviation of 78 when the count is 1000. Improving the accuracy by simply doubling the number of cells counted merely reduced the standard deviation to 72; but repeating the estimation with a second pipette and second counting chamber reduced the standard deviation to 55. However, it is only fair to point out that the second method involves more work than the first.

Details of the Size of the Error in Blood Counts.

Before concluding this section I should like to list the errors that may be expected when one carries out counts on samples of blood containing from 100 to 1400 red cells in the volume counted. This will be done on the assumption that only one pipette and one counting chamber are used in each case. The total variances will then be those listed in Table I. From these one can calculate the standard errors by taking the square root of the variances. If one assumes that a number of counts performed on the same specimen of blood would give a normal distribution of values, one can then calculate the limits within which the counts will be expected to fall with certain stated frequencies. For example, one would expect to find a count five times in 100 that differed from the true count by at least 1·96 times the standard deviation; and one would expect a count once in 100 times, on the average, that differed from the true count by at least 2·58 times the standard deviation. The detailed figures have been tabulated in Table II.

Table II can be interpreted in the following way. If the true count in a particular specimen is 600 cells, the table indicates that anyone who made many counts on this specimen, with as much skill and as good apparatus as Berkson and co-workers used, would not, on the average, obtain results lower than 511 or higher than 689 more than five times in 100. Similarly, he would not obtain counts lower than 483 or higher than 717 more than once in 100 times.

Lists similar to that in Table II can be drawn up in cases in which more than one pipette or more than one counting chamber is used. The general formula for the

TABLE I.

Variance of the Distribution of Erythrocyte Counts when Different Numbers of Cells are Counted.

Total Number of Erythrocytes Found in $\frac{1}{5000}$ Cubic Millimetre of Blood (n).	Red Blood Cell Count in Millions per Cubic Millimetre.[1]	Variance Due to Random Sampling V_s ($=0{\cdot}8464n$).	Variance Due to Error of Pipetting V_p ($=0{\cdot}002209n^2$).	Variance Due to Error in Using Counting Chamber V_c ($=0{\cdot}002116n^2$).	Total Variance
100	0·5	85	22	21	128
200	1·0	169	88	85	342
300	1·5	254	199	190	643
400	2·0	339	353	339	1031
500	2·5	423	552	529	1504
600	3·0	508	795	762	2065
700	3·5	592	1082	1037	2711
800	4·0	677	1414	1354	3445
900	4·5	762	1789	1714	4265
1000	5·0	846	2209	2116	5171
1100	5·5	931	2673	2560	6164
1200	6·0	1016	3181	3047	7244
1300	6·5	1100	3733	3576	8409
1400	7·0	1185	4330	4147	9662

[1] This column can be readily altered if a different area of the grid has been used. The figures would be doubled, for example, if the cells in $\frac{1}{10,000}$ of a cubic millimetre of blood had been counted.

total variance is $\frac{n^2}{1,000,000}\left(\frac{846,400}{n}+\frac{2116}{c}+\frac{2209}{p}\right)$ where n is the number of blood cells counted, c is the number of counting chambers used, and p is the number of pipettes used.

Finally, two warnings should be issued in regard to the use of the tables already given. (i) It has been assumed in the compilation of Table II that the errors of using the pipette and counting chamber are distributed normally. This assumption may be accepted fairly readily in view of the fact that errors made in the use of measuring apparatus are commonly believed to conform to the normal distribution; but the assumption has not been tested carefully in the case of the hæmocytometer. (ii) Predictions of the error of blood counting have been made in terms of what are normally the three most important constituent errors. However, even in the discussion of these it has been necessary to lay down certain limiting conditions before a numerical value could be given to the errors. But one should not overlook the possibility that a worker may, in all innocence, make mistakes of a private and unexpected character.

Errors in the Counting of Leucocytes in a Hæmocytometer.

It is scarcely worth while constructing separate tables to show the errors involved in counting leucocytes in the hæmocytometer. The standard deviation due to random sampling is some 9% larger, owing to the absence of an "overcrowding" effect. Otherwise the errors are comparable with those found in the case of red blood cells.

Errors Made in Performing a Differential Leucocyte Count.

The errors involved in making a differential leucocyte count may be listed as follows. (i) There is an error of chance distribution comparable in type with that described by "Student" in the case of hæmocytometer counts. Once again this is an unavoidable error. It can be decreased by counting large numbers of cells, but it is present in the results of even the most careful workers. (ii) There is the possibility that error may result from the wrong classification of cells. This can be reduced by care and experience in the making, staining and examination of blood films. I do not propose to discuss it further. (iii) An error may arise because the sample of cells classified is not a random sample of those present on the slide.

Error of Chance Distribution.

Suppose that the true percentage of a certain leucocyte in a specimen of blood is p, and we are considering errors that arise in classifying a random sample of leucocytes so as to estimate p. Then in a large series of counts the average value obtained would be close to p and the variance of the various estimates of p would be given by the formula $\frac{p(100-p)}{n}$, where n is the total number of cells classified. For example, if the true value of p is 40% and 400 cells are classified, then the variance of p is $\frac{40\times 60}{400}$ or 6, and the standard error is consequently 2·45. Now this standard error multiplied by 1·96 is equal to 4·8. Hence if we

TABLE II.

Estimated Size of the Error Involved in the Counting of Various Numbers of Red Blood Cells with the Hæmocytometer.

Number of Cells Counted.	Variance.	Standard Deviation.	1·96 × Standard Deviation.	2·58 × Standard Deviation.	Limit Below Which Count Would Not be Expected to Fall More than Five Times in 200.	Limit Above Which Count Would Not be Expected to Fall More than Five Times in 200.	Limit Below Which Count Would Not be Expected to Fall More than Once in 200 Times.	Limit Above Which Count Would Not be Expected to Fall More than Once in 200 Times.
100	128	11·3	22	29	78	122	71	129
200	342	18·5	36	48	164	236	152	248
300	643	25·4	50	66	250	350	234	366
400	1031	32·1	63	83	337	463	317	483
500	1504	38·8	76	100	426	576	400	600
600	2065	45·4	89	117	511	689	483	717
700	2711	52·1	102	134	598	802	566	834
800	3445	58·8	115	152	685	915	648	952
900	4265	65·3	128	168	772	1028	732	1068
1000	5171	71·9	141	186	859	1141	814	1186
1100	6164	78·5	154	203	946	1254	897	1303
1200	7244	85·1	167	220	1033	1367	980	1420
1300	8409	91·7	180	237	1120	1480	1063	1537
1400	9662	98·3	193	254	1207	1593	1146	1654

assume that the various experimental values of p have a normal distribution, we should expect that in 95 cases out of 100 the experimental result would, on the average, lie in the range $(40-4{\cdot}8)$ to $(40+4{\cdot}8)$, that is, in the range 35·2 to 44·8.

By similar calculation one could ascertain, to any desired degree of probability, the limits within which differential counts would be expected to fall if one was given the true percentage of the cell under consideration and the total number of cells classified; or, what would be more relevant to a practical situation, given an experimental result, one could estimate the probability that the true result was actually some nominated value.

It is easy to demonstrate that the standard error for any given value of n is relatively smallest when p equals 50%, and the standard error for $(50+x)\%$ is the same as that for $(50-x)\%$.

Bias in Sampling from Leucocytes on Slide.

If the leucocytes which one classified in the course of a count were an unbiased sample of those on the slide, then the error of counting, in the case of careful workers, would simply be the error already discussed. Plum (1936) and Barnett (1933) and others have produced results which support the view that the total error of differential counts can be explained in this way.

Not everyone agrees with this, for there is the possibility that the results of a count are influenced by the particular portion of the blood smear that has been evaluated. The edges and tail of the smear show different proportions of leucocytes from the body of the smear. MacGregor, Richards and Loh (1940) conclude that the results vary according to whether the hæmatologist counts the leucocytes in the edges only, or moves backwards and forwards over the full width of the film, or uses some other methods, such as the so-called "palisade" or "battlement" technique. They believe that the palisade method gives results that correspond most closely with the true count; but their conclusions are based on data from normal subjects and may not apply in various pathological conditions.

A partial solution of the two conflicting views about the errors in the differential count is provided by Mainland, du Bilier and Stewart (1935). They suggest that the discrepancy between the true value and the estimated value probably differs from one worker to another, and they advise that the important thing is "a determination by each worker of the variations due to sampling and technique between percentage counts made by whatever method the worker regularly uses". Each worker should perform duplicate counts from time to time and obtain an estimate of the discrepancies that can be explained by his technique.

Error in Counting Absolute Number of a Given Type of Leucocyte.

The information from the differential leucocyte count is generally combined with that from the total count to give the absolute numbers of the various leucocytes per unit quantity of blood. This is usually desirable and often essential if the change in a particular type of leucocyte is to be followed correctly.

It may sometimes be required to calculate the variance of such absolute numbers. This reduces itself to the problem of calculating the variance of a product when one knows the variance of each of the two independent factors. If the variance of p is V_p and that of n is V_n, then the variance of pn is $p^2V_n + n^2V_p$. It is true that the variance of each of the two factors in the absolute count is related to the technique of counting; but for the purpose of the following calculation we shall assume that the variances have their minimum values, which we shall call t in the case of the total count, and $\frac{p(100-p)}{n}$ in the case of the differential count; t is the number of cells counted in the total leucocyte count and may be taken as 400; n is the number of cells classified in the differential count and may also be taken as 400; p is the percentage of, say, eosinophile cells, and may be reckoned as 4.

Suppose we consider the variance of the absolute number of eosinophile cells per cubic millimetre. The variance of the total count of 400 is 400; and the variance of the percentage count of 4 is $\frac{4\times 96}{400}$ or 0·96. Hence the variance of the product obtained by multiplying the 400 and 4 together is $400^2 \times 0{\cdot}96 + 4^2 \times 400$, or 160,000, and the standard error is 400. The standard error is then 25% of the product itself. The product referred to, namely 1600, would have to be multiplied by a constant to convert it into absolute numbers of eosinophile cells per cubic millimetre of blood; but since the standard error would be multiplied by the same constant, the step may be omitted. Hence the standard error of the absolute number of eosinophile cells is 25% of the absolute number; that is, it is very large.

These considerations point to a more accurate way of counting eosinophile cells—the direct method. In this technique the differential leucocyte count is dispensed with and the eosinophile cells are recognized as such in the hæmocytometer chamber and counted directly. The chamber used is the Fuchs-Rosenthal variety, and the diluting fluid contains an eosinophilic stain. If 16 eosinophile cells were counted, the standard error would be 4, so that the accuracy obtained would be the same as that above. However, in the usual case it is possible to count about 80 to 100 eosinophile cells with the same amount of work as would be needed for a total leucocyte count. Hence by using the direct method one saves the labour of a differential count and improves the accuracy of the estimation. It is this latter point that is the more important, for the differential count gives more information than that relating to eosinophile cells and will continue to be used except in those cases in which accurate information about the numbers of a particular type of leucocyte is necessary. Moreover, it should be mentioned that the older method of deriving the absolute numbers of eosinophile cells is often adequate when one is examining a group of subjects to detect some marked change from normal in the number of eosinophile cells. For example, the eosinopenia that follows the injection of adrenaline was shown strikingly in the course of the examination of 18 subjects by White, Ling and Klein (1950), using combined total and differential counts. These authors point out that other investigators had data from which the same conclusion could have been drawn, but the data were passed over, presumably because the workers lacked sufficient faith in the indirect method of counting rare leucocytes.

Eosinophile cells have been used in the above illustration for two reasons. One is that the advantage of direct counting of individual types of leucocytes is relatively greater in the case of the rarer leucocytes. The other is that the method can be applied only to those leucocytes which can be identified in the hæmocytometer chamber. Lymphocytes and monocytes cannot be accurately distinguished from one another or from other mononuclear cells in the hæmocytometer, and so the method cannot be applied to them.

SUMMARY.

1. The error due to chance distribution of the cells in a hæmocytometer cannot be eliminated; but it can be reduced in relative size by increasing the number of cells counted.

2. If the hæmatologist uses different pipettes or different counting chambers from time to time, he introduces a second important source of errors. These errors are not decreased relatively by the counting of more cells. In an average case they are each as important as the error of chance distribution when 400 or more cells are counted.

3. Tables are given for computing the contribution of each of these main errors towards the total, and the assumptions underlying the use of these tables are discussed.

4. In a differential count there is an inevitable error due to the chance distribution of the various types of cell in the sample of blood obtained.

5. There may in addition be an error due to the way in which the different types of leucocyte are distributed over the various parts of the blood film.

6. It is an advantage to use the method of direct counting of leucocytes whenever feasible.

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THE ADRENALS IN THE RHEUMATIC DISEASES.[1]

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THE accomplishments of surgery since the days of Lister have been glorious and spectacular, whilst those of medicine for a while seemed to lag behind. However, the ever-widening field of organic chemistry and especially biochemistry opened up a wonderful vista to the physician, giving him an insight into a few of the intricate workings of the human body and providing him with potent chemical tools of trade.

These secrets of nature were not yielded up without vast amounts of observation and work, trial and error. The continual exploration of the unknown calls for tenacity of purpose, constancy of resolve and a continually receptive and inventive mind. Today, however, the intricate nature of many problems calls for team-work, which is possible only at certain places in the world where knowledge and technical efficiency have reached the highest plane of development. The discovery of compound E, 17-hydroxy-11-dehydrocorticosterone, was possible only by a skilled steroid chemist and physician and its clinical application by an indefatigable brilliant pursuer of an undimmed objective, whilst its production on a commercial scale can be achieved only by a chemical firm with vast resources and a high standard of chemical research and attainments, owing to the difficulties of synthesis.

THE ADRENAL MEDULLA: SOME PHYSIOLOGICAL FEATURES.

Epinephrine (adrenaline) isolated in 1902 by Abel from the adrenal medulla, is probably formed from tyrosine and from phenylalanine. In spite of the years which have elapsed since its discovery, Soffer has remarked that "despite our extensive knowledge of the actions of epinephrine, its actual function in the body is obscure". The medulla of the adrenal gland is not indispensable to life. The effect of adrenaline on vascular tonus, carbohydrate metabolism and the "emergency function", as elaborated by Cannon, are well observed phenomena. Grollman suggested that adrenaline might act synergistically with the more vital and destructible cortical hormone. The vascular tonus, the disturbances in carbohydrate metabolism and the loss of the "emergency response" are all corrected by potent cortical extracts or certain fractions of the adrenal cortex.

Long and Fry showed that there was an unmistakable fall in adrenal cholesterol and ascorbic acid content after the subcutaneous or intravenous administration of epinephrine, this effect being abolished by the removal of the hypophysis. This pointed to the production of the adrenocorticotropic hormone of the anterior pituitary lobe—namely ACTH—which stimulated adrenal cortical activity as revealed by the fall in cholesterol and ascorbic acid levels, two substances probably bound up in the synthesis of the cortical hormones. Various traumata, such as exposure to cold, hæmorrhage, fractures, injuries to muscle, operative procedures, burns, *et cetera*, cause a prompt increase in the formation of adrenal cortical fractions. These same stresses cause an increase in epinephrine, and it is reasonable to assume that the increased adrenal cortical secretion is due to the adrenocorticotropic hormone of the anterior pituitary lobe (ACTH) liberated by adrenaline. The chromaffin granules of the medulla discharge a few moments after exposure to an alarming stimulus, and thus epinephrine is apparently the first hormonal response in the alarm reaction of Selye, which leads later to cortical response.

Epinephrine has two actions on the adrenal cortex, the first direct, within a few minutes and short in extent, and the second indirect, mediated by way of ACTH, much longer in duration and taking longer to initiate. The former action is directly on the cortical cells, the latter on the anterior pituitary lobe, resulting in the production of ACTH, which in turn stimulates the adrenal cortical cells.

Epinephrine increases cardiac output and the heart rate. It also produces contraction of the blood vessels of the skin, the mucous membranes and the cerebrum, but dilatation of the coronary blood vessels and the arterioles of striated muscle.

These few observations indicate that adrenaline may be valuable in rheumatoid arthritis by its stimulation of the adrenal cortex by way of the pituitary. I have found it of great value in conjunction with "Proseptasine" therapy in rheumatoid arthritis and ankylosing spondylitis associated with fever, and in the treatment of a number of patients presenting the typical vasospastic changes. Its administration must be continued for a prolonged period, six to twelve months, and in a few cases it has produced untoward symptoms such as elevation of the blood pressure. The dosage employed is generally 0·5 to 1·0 millilitre of adrenaline (1 in 1000), preferably in oil, twice a day or even four times a day in febrile rheumatoid arthritis.

THE ADRENAL CORTEX.

The cortex is of great importance, being indispensable to life, in contrast to the medulla, which is not essential to life. Its steroids are concerned with electrolyte, carbohydrate and sex metabolism.

The Hormones of the Adrenal Cortex.

The first attempt at substitutive therapy in the treatment of the destructive diseases of the suprarenals was made about 1857, and in the third decade of this present century different forms of extract helped to prolong the life of the adrenalectomized animal and of humans afflicted by Addison's disease. Under the stimulus of this success many workers attempted the isolation of the various crystalline fractions of the whole extract, great progress being made from 1936 to 1946. At present there are 28 steroid hormones which have been isolated from the adrenal cortex, and probably more will be found in the future.

[1] Read at a meeting of the Australasian Association of Physical Medicine (British Medical Association) at Melbourne, October, 1949.

Soffer lists the active fractions isolated from the whole adrenal cortical extract as follows:

- Whole Adrenal Cortical Extract.
  - Crystalline Fractions.
    1. Desoxycorticosterone.
    2. Corticosterone.
    3. Dehydrocorticosterone.
    4. 17 - hydroxy - 11 - dehydrocorticosterone (compound E of Kendall).
    5. 17 - hydroxycorticosterone (compound F of Pfiffner and Wintersteiner).
    6. 17 - hydroxy - 11 - desoxycorticosterone.
  - Amorphous Fraction.

Those outlined above have important physiological significance. The sex steroids, especially the androgens, may be important in gout, the latter being named the "N" (nitrogen-retaining) corticoids.

Desoxycorticosterone causes retention of sodium, chloride and water, whilst it increases the excretion of potassium and phosphorus. It has no effect on carbohydrate metabolism. The low blood pressure in Addison's disease is restored to normal by this steroid, which can also produce hypertension in such an individual with cortical destruction but not in a normal person. This compound is concerned with the electrolyte metabolism and by itself has no beneficial effect in rheumatoid arthritis. On the contrary, Selye has produced arthritis by this hormone in adrenalectomized animals subjected to unilateral renal arterial compression and given large quantities of salt.

Corticosterone, dehydrocorticosterone and 17-hydroxy-11-dehydrocorticosterone (compound E—cortisone) are concerned with carbohydrate metabolism, correcting defects in the carbohydrate metabolism of adrenalectomized animals. Storage of glycogen in the liver, increase of blood sugar levels and the prevention of hypoglycæmia follow the injection of hormones. Compound E of Kendall (cortisone) has the most pronounced effect on carbohydrate metabolism and will in addition restore the ability of the adrenalectomized rat to form glucose from lactic and pyruvic acids. Corticosterone and dehydrocorticosterone produce a very slight retention of blood sodium.

17-hydroxycorticosterone (compound F) has a pronounced effect on carbohydrate metabolism, and also, like compound E, induces a negative sodium balance.

The amorphous fraction has a potent effect on the distribution of electrolytes, but not on carbohydrate metabolism.

The hormones corticosterone, dehydrocorticosterone, 17-hydroxy-11-dehydrocorticosterone and 17-hydroxycorticosterone are called the 11-oxysteroids because they have an oxygen atom at C11, and are also called glycogenic corticoids because they deposit glycogen in the liver of adrenalectomized animals if given hypodermically. They are concerned with the breakdown of protein into amino acids and glucose, and with synthesis of the latter to glycogen, which is deposited in the liver. They therefore increase the blood sugar levels in adrenalectomized animals and prevent hypoglycæmia, and are designated by some writers as the "S" or sugar corticoids.

Sex Steroids.

The Relation of the Adrenals to the Urinary Excretion of the Neutral Ketosteroids.—The term "17-ketosteroids" is official to the steroids with a ketone group on the seventeenth carbon atom. They form the urinary products of androgenic metabolism, being derivatives from substances produced by the male gonads and the adrenal glands. They are divided into α and β ketosteroids; the former are derived from male gonads and the adrenals, whilst the latter are adrenal in origin. Adult men excrete on an average about 15 milligrammes per day whilst women excrete about 10·2 milligrammes. The amount excreted is low in malnutrition, *anorexia nervosa*, anæmia, infections and liver disease, and extremely low in Addison's disease and Simmonds's disease, but increased in hyperplasia of the adrenal cortex or tumours and in Cushing's syndrome. Their excretion has been reported as being increased in ankylosing spondylitis, but this has been denied by a few workers.

The Relation of the Adrenals to the Urinary Excretion of Glycogenic Corticoids.—Glycogenic steroids, as was stated previously, are those possessing activity in carbohydrate metabolism. Venning and Browne, using the Reinecke-Kendall test, a biological assay technique, investigated and measured one type of adrenal cortical function. The ability of certain adrenal corticoids to deposit glycogen in the livers of fasting adrenalectomized mice is the basis of the test. The substances giving this reaction exercise an effect exclusively on carbohydrate and protein metabolism and are derived from the adrenal cortex. They are labile substances, and the amount excreted in the urine probably represents a small fraction of the total amount elaborated in the adrenal gland. The excretion of corticoids is higher in men than in women. Their importance is revealed by the fact that, although the newborn infant has infinitesimal amounts, the adult level of excretion is reached at the age of two and a half years. The average male excretes 40 to 85 glycogenic units per millilitre of urine, whilst the average female excretes 25 to 55 units per millilitre. In Addison's disease and in hypopituitarism there is a pronounced reduction, whilst in Cushing's syndrome the amount excreted is frequently elevated to several hundred units. Compound E has been shown by Hench and his colleagues to produce Cushing's syndrome when administered in large amounts to patients suffering from rheumatoid arthritis. As yet no figures are available as to the amounts of these corticoids excreted by sufferers from rheumatoid arthritis or allied diseases. However, pregnancy, especially late pregnancy, and muscular activity are accompanied by increased excretion of the corticoids. Infection, injury and surgical procedures and any condition which produces increased cortical function will increase the excretion of these corticoids. These conditions just enumerated will cause a remission of rheumatoid arthritis.

The glycogenic unit is equivalent to the biological activity of one microgramme of compound E of Kendall.

The results revealed by the biological assay of the glycogenic corticoids parallel the urinary excretion of the 11-oxysteroids as determined by Talbot's colorimetric method. The amount excreted is increased in Cushing's syndrome, in severe burns, after extensive operative procedures or in adrenal cortical virilism, and greatly increased in pregnancy.

Certain Conditions which Relieve or Cause a Remission in Rheumatoid Arthritis.

In a successful thesis for the Sir Charles Hastings Clinical Prize in 1940, I recorded that the following factors had been noted by myself to relieve or cause a temporary remission of rheumatoid arthritis: pregnancy, febrile states such as pneumonia, jaundice, starvation, and operative procedures. Many authors, both before and after I recorded these observations, have recorded similar findings.

Philip Hench, in an informative article on the potential reversibility of rheumatoid arthritis, revealed that pregnancy and jaundice would relieve 60% to 90% of patients, reversing the disease, which, however, recurred later.

Pregnancy produces an increase not only in the suprarenal cortex, but also the pituitary gland.

Soffer detailed the following conditions which produce an increase in the size and function of the suprarenal gland: (*a*) Endocrinological factors, such as the adrenocorticotropic hormone of the anterior lobe of the pituitary, thyroxine, œstrogens, castration in the male, and insulin. (*b*) Pathological factors, such as increased protein catabolism, complete inanition, shock, burns, anoxia, acute and chronic infections, tumours associated with cachexia, vitamin *B* and *C* deficiency states, and unilateral adrenalectomy. Some of these conditions undoubtedly act as an alarming stimulus on the adrenal medulla. (*c*) Miscellaneous factors such as exercise, a diet rich in protein, late pregnancy and the puerperium, injections of cholesterol or a diet rich in cholesterol, and various noxious

agents (cold, adrenaline *et cetera*). It is interesting that injections of cholesterol have no influence on rheumatoid arthritis, as has been revealed by Hench and his colleagues.

I have employed for a number of years insulin and glucose in the treatment of rheumatoid arthritis, and in 1937 I recorded my experience of such therapy on patients exhibiting typical vasospastic phenomena such as pallor and cyanosis, whilst in 1940 I described the use of adrenaline as being extremely valuable in febrile types of the disease, its use producing rapid defervescence.

As has been stated previously, we know now that adrenaline stimulates cortical hyperplasia by way of the anterior pituitary lobe and fails to do so after hypophysectomy. Thyroxine and the œstrogens also act by way of the pituitary. Protein catabolism as occurring in starvation, cachexia associated with neoplasm, burns, operations and various traumata increase adrenal cortical hypertrophy.

If a sudden increase of available protein occurs, from either an exogenous or an endogenous source, there is a corresponding increase in adrenal cortical function and size. There appears to be a correlation between gland mass and the rate of hormone secretion.

Whole adrenal cortical extract and desoxycorticosterone, when injected continually over a long period into a normal animal, have been shown to produce adrenal cortical atrophy.

Adrenal cortical atrophy can occur in Simmonds's disease, and I have noted associated rheumatoid arthritis in two such cases.

Swann, in reviewing the pituitary adrenocortical relationship, drew attention to the control exerted by the pituitary over the adrenal cortex with regard to protein, carbohydrate and fat metabolism. ACTH stimulates the production of sex, electrolytic and carbohydrate steroids. The hypoglycæmia of the hypophysectomized rat is promptly altered by adrenal cortical extract and the glycogen content of the liver restored to normal.

Starvation in the rat increases the adrenal cortex, but only in the presence of an intact pituitary. Adrenaline produces an increase in the size of the adrenal cortex, but only by way of the pituitary gland. Insulin will produce an increase in adrenal cortical size by way of the adrenal medulla and pituitary gland. ACTH is the hormone whose production is stimulated by these various factors.

Relation of the Adrenals to the Gonads.

Male castration in the animal world is followed by adrenal cortical hypertrophy. It has been found in animals that androgens cause very little alteration in adrenal size and may produce atrophy. It has also been found that progesterone in large amounts produces considerable atrophy of the adrenal cortex. I have seen this hormone tried recently in rheumatoid arthritis, but experimentally it is dangerous. It has also been found that œstrogenic compounds uniformly cause pronounced hypertrophy of the adrenals, but in contrast to the action of adrenaline there is no evidence of increase of the cortical lipins. However, in spite of these results of animal experiments, we find that females are more susceptible to rheumatoid arthritis than males, and further, that the urinary corticoid excretion, which reflects the amount of production of the carbohydrate hormones of the cortex, is higher in men than in women. Œstrogenic compounds apparently do not produce an increase in the glycogenic corticoids.

The Thymus and the Adrenal Gland.

Both compound E and ACTH produce thymic atrophy, the latter probably by way of the former.

Thymectomy in the experimental animal or thymic atrophy produced by irradiation will bring about hypertrophy of the suprarenal cortex. The frequent occurrence of diffuse lymphoid hyperplasia in Addison's disease, together with thymic enlargement and the infiltration of many organs with lymphocytes, may suggest trial of thymic irradiation by X rays in rheumatoid arthritis. The widespread distribution of nodules composed of lymphocytes and plasma cells seen in rheumatoid arthritis and other diseases may be due to thymic over-activity. Compound E will produce a rapid dissolution of these lymphocytic accumulations and disappearance of the nodules, as revealed by Hench and his colleagues. In Still's disease splenic enlargement and lymphatic hyperplasia are common, as can be readily seen by palpation of axillary, inguinal and epitrochlear glands. Some interesting speculations may thus be made. May such enlargements be concomitants of thymic hyperplasia? There may be a suppressive action by the thymus in rheumatoid arthritis preventing the rapid and sufficient production of compound E, or its utilization by the body tissues, even though the histological examination of the adrenals reveals no abnormality in severe cases of the disease. Compound E may in large doses inhibit thymic over-activity, and it may be of some significance that lymphatic accumulations in various tissues, as observed in rheumatoid arthritis, are subject to dissolution by this hormone.

However, on the other hand, rheumatoid arthritis is not very common in Addison's disease, although Curschmann in 1932 described three cases in which *arthropathia deformans*, without any evidence of tuberculosis, developed during the course of severe Addison's disease. ACTH produces thymic atrophy, but only in the presence of intact adrenals. It had been observed that excessive muscular exercise in the rat will induce adrenal enlargement and atrophy of the thymus. There is therefore an antagonism between these two glands, and in view of the profound effect of compound E on lymphocytic synovial nodules in rheumatoid arthritis, an investigation of the role of the thymus in Still's disease and rheumatoid arthritis may prove valuable. We are at present investigating this relationship. Dougherty and his co-workers have demonstrated that suprarenal cortical extract will produce dissolution of lymphocytes, probably releasing euglobulin—important in antibody formation.

However, E. Shipton and I have constantly found a high euglobulin level in patients with severe rheumatoid arthritis often unresponsive to any therapy. The question arises whether the lymphatic nodules and infiltrations, and the hyperplasia of the lymph glands seen in non-tuberculous atrophy of the adrenal cortex, and similar nodules *et cetera* found in rheumatoid arthritis, ankylosing spondylitis *et cetera*, are due to the same causative factor—an excessive thymic hormone, either absolute in the former group or relative in the latter. This is a natural question that flits across the stage of conjecture and possibilities, rendered pertinent because of the normal histological appearance of the adrenal cortex in rheumatoid arthritis and because of the normal blood response to adrenaline by way of the anterior lobe of the pituitary in the majority of cases.

The Effects of 17-Hydroxy-11-dehydrocorticosterone (Compound E—Cortisone) in Rheumatoid Arthritis.

The increase in the amounts of oxysteroids in the urine of pregnant women would have warranted their consideration as a therapeutic substance in rheumatoid arthritis.

Hench *et alii* stated that "it became increasingly difficult to harmonize the microbic theory of the origin of rheumatoid arthritis with the phenomenon of relief of the disease by jaundice or pregnancy". They believed that there was a common denominator to the various agents or states which relieved rheumatoid arthritis. Hench and his colleagues conjectured that the hypothetic common denominator or "anti-rheumatic substance X" was a biological compound normal to the human organism. They used for a brief period Kendall's cortical extract, having conjectured that the anti-rheumatic substance X might be an adrenal hormone. General anæsthesia and surgical operations relieved rheumatoid arthritis and were known to stimulate the adrenal cortex. Hench *et alii* became interested in Kendall's compound E, the most potent of the glycogenic corticoids, and began to treat their first patient in September, 1948, using 100 milligrammes of compound E by intragluteal injection. A rapid remission of the disease took place, and it was noted that a reduction of the dosage to 50 or 25 milligrammes led to recurrence of symptoms. They avoided psychological reactions by employing cholesterol and replacing it by compound E without allowing the patients or clinicians to know the date of alteration.

At first compound E was employed, but later on the acetate was found to be cheaper and more easily prepared. The later patients have been treated by dosage of 300 milligrammes on the first day and a subsequent daily dosage of 100 milligrammes. They observed that the minimal daily dose is 75 to 100 milligrammes and even this amount will not entirely control the symptoms and the sedimentation rate in all cases.

Clinical Effects.

The effects were noted in all the fourteen patients treated at the Mayo Clinic with compound E, with the acetate or with ACTH, and are as follows.

A pronounced reduction in pain and stiffness took place within a few days. In some cases improvement occurred in twelve hours or less. The dramatic improvement was almost unbelievable to one who has watched these patients for many years, and in my experience can be compared only with that once seen during an attack of pneumonia. The relief of pain and stiffness was followed by decreased articular pain and increased movement, with reduction of swelling of the joints. Deformities such as flexion deformity of the knee or elbow and inability to raise the arms over the head might disappear rapidly. Joint tenderness to pressure rapidly disappeared.

Muscular power returned quickly, and it was noted that the patients were able after a few days to do things which would have been absolutely impossible before compound E was administered, such as rising unaided from low seats, opening doors and climbing stairs *et cetera*.

Appetite returned rapidly and weight was gained—in one case 30 pounds, in another 21·5 pounds, in ten weeks.

The mental uplift was pronounced and often the patient could not sleep on the first night. This euphoria was accompanied by increased mental capacity.

All patients responded to compound E, some more than others, but when the hormone therapy was suspended the disease returned fairly promptly in all cases. However, in one case the erythrocyte sedimentation rate rose but the patient was symptomless five weeks after suspension of the treatment. It may be that prolonged administration will tend to prevent recurrence. After suspension of the hormone therapy and recurrence of the disease, a second course of therapy produced prompt relief again in all cases. In one case 100 milligrammes did not control the disease, and when larger doses were employed Cushing's syndrome occurred, with round face, purplish abdominal striæ, slightly elevated blood pressure, virilism and acne. Suspension of the hormone therapy produced reversal of these signs.

The erythrocyte sedimentation rate generally returned promptly to normal or near normal provided adequate dosage was maintained. In a few cases clinical improvement was much greater than the reduced erythrocyte sedimentation rate warranted.

Serum protein levels returned to normal if they had been deranged, and an abnormal albumin-globulin ratio was rapidly made normal.

Anæmia rapidly decreased and the red cell count and hæmoglobin value became normal.

The general appearance of the patient—the muddy complexion, seborrhœa, cold clammy hands, cyanosis of nails *et cetera*—returned to normal.

The excretion of corticosteroids is always increased when cortisone is being administered. A constant level of between 1·0 and 2·0 milligrammes is the rule when the daily dosage is 100 milligrammes; whilst normal people excrete 0·12 to 0·34 milligramme per day, the former level borders on that observed in Cushing's disease.

The urinary 17-ketosteroid excretion remained in the low normal or even in the subnormal range during cortisone administration. In one case over a period of three months it was reduced from a normal of approximately 10 milligrammes to 1·2 milligrammes.

Compound E increases the excretion of urate. Kendall has shown that 0·3 milligramme of desoxycorticosterone acetate exercises the same effect on electrolyte metabolism as does 10 milligrammes of compound E.

Compound E will increase the pH of the venous blood as observed in one case (7·3 to 7·45).

The hormone has produced amenorrhœa and may interfere with ovarian function.

After suspension of the hormone the disease recurs, but its readministration again produces a remission.

The Effect of ACTH on Rheumatoid Arthritis.

ACTH was tried in rheumatoid arthritis because it is the most powerful stimulant of the adrenal cortex.

The dosage employed was the same as with compound E—namely, 100 milligrammes—although in some later cases smaller doses have been used. In one case (not at the Mayo Clinic) a dose of 10 milligrammes four times a day was employed with success.

Mason, in experimental administration of ACTH to a normal young female, produced the following alterations in the urinary excretion of the cortin-like substances (Table I).

Table I.[1]

Duration of Administration in Days.	Amount of ACTH Administered. (Milligrammes.)	Quantity Excreted. (Milligrammes *per Centum*.)
6	25	0·255
6	50	0·387
10	100	1·44

[1] The quantity excreted prior to ACTH administration was 0·180 milligramme *per centum*.

The last amount excreted after the administration of 100 milligrammes approximates that observed in cases of Cushing's disease.

The results are just as striking with ACTH as with compound E as regards relief of symptoms, but the sedimentation rate decreased more promptly and steadily when the latter was used. However, once treatment was suspended, the symptoms and signs recurred promptly, and the sedimentation rate, which had plummeted to normal, rose almost as rapidly.

Ankylosing spondylitis responds just as rapidly as rheumatoid arthritis, the temperature (in one case over 100° F.) returning to normal in twenty-four hours, and this takes place with either compound E or ACTH. Pain, stiffness and soreness on pressure are rapidly reduced, and movement is increased.

ACTH produces an increase in the excretion of ketosteroids and oxysteroids.

ACTH will produce Cushing's syndrome, and the androgenic effect in females produces signs of virilism. However, the syndrome is reversible.

Both ACTH and compound F produce greater electrolytic changes than compound E.

To avoid these deleterious reactions, Hench suggested that the dosage might have to be reduced, with a view to their avoidance whilst clinical improvement was maintained.

Kendall thinks that the action of ACTH may be to liberate either compound E or compound F.

It was also found that a patient who responded to compound E would also respond after relapse to ACTH and *vice versa*. The two hormones are therefore interchangeable as regards their beneficial action in the disease.

Baker and Ingle found that ACTH might produce atrophy of the lymphoid tissue, epiphyseal cartilage, hair and epidermis. It will retard chondrogenesis and osteogenesis in immature rats and antagonize the growth hormone. It will produce atrophy of the red marrow with apparent replacement of it by fat. These changes produced in the growing rat by the hormone sound a note of caution when such therapy is considered for any continued period in children.

EFFECT OF COMPOUND E AND ACTH ON RHEUMATIC FEVER.

Rheumatic fever is also altered rapidly by both hormones. The fever is first affected, followed by the polyarthritis, the tachycardia, and the abnormal electrocardiographic changes. The rapid return of these changes to normal is accompanied by a quick reduction in the erythrocyte sedimentation rate. The same mental uplift takes place as in the other diseases treated. The leucocyte count and the serum protein levels follow the same course. The dosage may have to be higher in rheumatic fever, and in one case 200 milligrammes of cortisone were given for ten days, in another for nineteen days. ACTH was given in smaller doses. In two cases, however, there was no recurrence after the drug was suspended, in one case twenty-one days later, and in the other eighteen days later. The sedimentation rate had not risen again in these two cases. In the third case there was a recurrence, but the patient again responded promptly to the hormone. If these results indicate that a large number of patients suffering from rheumatic fever will not relapse after the suspension of the hormone, a tremendous forward advance in the treatment of rheumatic fever has been achieved. If this result is borne out by more extensive trials, one may conjecture that it could be due to the disappearance of the hæmolytic streptococcus, the antigen which initiates the disease, the antigen-antibody vicious circle having been broken by the hormones. The absence of recurrence would then be due to the absence of the antigen. On the other hand, the short duration of the disease may account for its successful outcome.

Selye has stated that "there is very convincing evidence that in combating damage during the alarm reaction, the sugar active corticoids are much more effective than the salt active corticoids". Damage during the alarm reaction by stimulating the sugar corticoids produces a remission in rheumatoid arthritis.

DISCUSSION OF COMPOUND E AND RHEUMATOID ARTHRITIS.

There are no available data on the oxysteroid excretion in rheumatoid arthritis, and biochemical results are awaited with expectancy. However, as was stated previously, in Addison's disease, in which the excretion is greatly reduced, rheumatoid arthritis is an uncommon complication, and thymic hyperplasia is a common accompaniment of the former.

In rheumatoid arthritis all histological examinations of the suprarenal gland, even in the case of old debilitated patients who have suffered from chronic rheumatoid arthritis and have died, fail to show any abnormality. In an adrenalectomized animal compound E restores the low blood sugar level to normal, but in rheumatoid arthritis there is not an abnormally low blood sugar level, and this does not suggest lack of cortisone.

A possible explanation of the beneficial effects of large doses of compound E may be that in rheumatoid arthritis an inhibiting substance is present, which can be overcome only by massive doses of the hormone. I have suggested in this paper that the thymus gland may act as an inhibiting agent, and radiation therapy should be given a trial in the care of adults. The key to therapy may yet lie in the thymus. George Thorn and his colleagues showed that ACTH in normal subjects and in patients with intact adrenals stimulates the secretion of electrolyte-regulating, carbohydrate-controlling and androgenic adrenal steroids. The increased secretion of the 11-oxysteroids is revealed by a fall in the number of circulatory eosinophile cells to 50% or more and an increase in the excretion of uric acid. Adrenaline, which stimulates the production of ACTH, will produce similar changes. In the majority of cases of rheumatoid arthritis the suprarenal gland responds normally to such stimulation even though the disease is severe.

Thorn *et alii* showed that 40 milligrammes of ACTH given for six days intramuscularly to a male subject, aged forty-six years, in four equally divided doses, caused a number of changes, amongst which were the following: (i) increased 11-oxysteroid excretion (sevenfold); (ii) increased uric acid excretion (102%); (iii) decreased sodium excretion (68%); (iv) decreased serum uric acid level; (v) increase in polymorphonuclear leucocytes; (vi) decrease in lymphocytes and eosinophile cells.

Kendall has shown that after adrenalectomy animals are easily affected by chill, heat *et cetera*, and cortisone restores the animal to normal. He suggests that in rheumatoid arthritis there may be a relative deficiency.

Levine has shown that patients afflicted by rheumatoid arthritis react to heat like normal people and that from the point of view of stress these people react as ordinary individuals.

The increased urate excretion without very much alteration in the serum uric acid content, the normal pattern of reaction to compound E by normal people, suggests that the hormone produces a pronounced nucleo-protein breakdown. For this reason both this hormone and ACTH are useful in acute gout in aborting the attack, but must be followed by colchicum to prevent recurrence.

CONCLUSION.

The brilliant response to cortisone and ACTH is a forward step of great significance in the therapeutics of the rheumatic diseases and may unlock the doors of other diseases. Elucidation of the *modus operandi* of their effect and the intricate mechanism through which they produce such results, now unknown, is awaited by the medical profession with eagerness. The fillip of these discoveries should stimulate us all to try to elucidate the ætiology and further the therapeutics of these diseases. These remedies will be scarce and costly for quite a long time and will need expert administration and a knowledge of their untoward reactions.

While we wait for such remedies, which produce at present a remission but not a cure, we should remember those measures which produce stimulation of the adrenal cortex—namely, the administration of insulin, adrenaline and a diet rich in protein, and exercise. Zeckwer showed that epinephrine and insulin will both produce enlargement of the adrenals and involution or shrinkage of the thymus and mesenteric lymph glands. Insulin hypoglycæmia is known to result in the discharge of endogenous adrenaline, and this hormone activates the adrenal cortical-lymphatic tissue reaction.

The effect on the blood when adrenaline is employed lasts about four to six hours; therefore in acute rheumatoid arthritis *et cetera*, the administration of 0·5 milligramme of adrenaline every four hours may be necessary. In the treatment of rheumatoid arthritis with great loss of weight, I have, during the last eighteen months, employed with great benefit insulin and adrenaline together. Administration may be continued for twelve months or more. These measures can easily be added to the armamentarium of the rheumatologist, whether he employs or believes in the sulphonamides, gold therapy or other forms of treatment. While these fall short of the spectacular achievements of cortisone and ACTH, they have a beneficial action and a scientific basis for their employment as remedies in these diseases.

SUMMARY.

Some pertinent physiological facts concerning the suprarenal medulla are considered, the action of adrenaline on the suprarenal cortex being both direct and indirect by way of the anterior lobe of the pituitary. This action is considered to be the first hormonal response in the alarm reaction of Selye.

The important hormones of the suprarenal cortex are indicated, especially those concerned with sugar metabolism, some of which are valuable in rheumatoid arthritis.

The terms ketosteroids, glycogenic corticoids and 11-oxysteroids are explained.

Conditions which produce a remission of rheumatoid arthritis are detailed, as well as those factors responsible for the enlargement of the suprarenal gland.

The pronounced effect of compound E and ACTH on the thymus is indicated, and some suggestions as to therapy are made. The absence of rheumatoid arthritis in Addison's disease is stressed.

The dramatic effect of cortisone in rheumatoid arthritis, as seen at the Mayo Clinic in 1949, is given in some detail, the rapidity of and changes associated with the remission being especially indicated. It is noted that the minimum dosage required was 100 milligrammes, which is ten times the amount required to control Addison's disease.

ACTH is able to produce the same rapid remission as cortisone, its effect being by way of the suprarenal cortex. The deleterious effects of both hormones are indicated.

It is noted that ankylosing spondylitis responds as well as rheumatoid arthritis, but both recur rapidly after suspension of the hormones. However, in rheumatic fever a recurrence has not been observed in two cases. This may indicate that a cure of rheumatic fever has been discovered. A suggestion is put forward that an antigen-antibody reaction may have been effectively broken by the hormones in rheumatic fever, in contrast to that of ankylosing spondylitis and rheumatoid arthritis.

The mode of action of these hormones is unknown, and future biochemical research may unlock valuable secrets of outstanding importance in medicine.

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Reports of Cases.

A CASE OF CARCINOMA OF THE URETER SUCCESSFULLY TREATED BY NEPHRECTOMY AND URETERECTOMY.

By RICHARD FLYNN AND H. HARRIS,

Sydney.

THE rarity of primary carcinoma of the ureter, and the still greater rarity of cure in this condition, have prompted the report of the following instance, in which the patient is still in good health some four years after radical removal of the tumour.

J.B., a male subject, aged seventy-five years, was admitted to the Royal Prince Alfred Hospital on April 2, 1946, with a history of intermittent hæmaturia of three weeks' duration. Prior to this episode the patient had been in excellent health and he had no history of previous genito-urinary disorder. The period of hæmaturia began with an attack of right-sided abdominal pain, which lasted for no more than a few seconds, but was soon replaced by severe pain in the right testis. Micturition, some minutes later, was associated with considerable difficulty, and resulted in the passage of what the patient described as pure blood. A variable amount of blood continued to be present in the urine until the time of operation. While the patient remained under observation there was no recurrence of the abdominal pain, but the localized pain in the testis persisted and there was frequent dysuria, mainly in the form of spontaneous interruption of the stream and difficulty in initiating the stream. At the time of his admission to hospital the patient's general health was good and there was no evidence of any disorder other than that under consideration.

On physical examination, a firm ballottable mass about two inches in diameter was palpated just to the right of the umbilicus. The bladder was distended to a level one inch above the pubes. Systematic examination failed to reveal any other sign of genito-urinary or abdominal disease. A catheter was passed and left *in situ*. Pathological investigation of the urine on April 5, 1946, showed it to contain 90% blood and 4% pus; a pure culture of hæmolytic *Staphylococcus aureus*, coagulate-positive, was obtained. Routine hæmatological investigation on April 3 showed that the hæmoglobin value was 96%, and that the leucocytes numbered 7700 per cubic millimetre. On April 5 the blood urea level was 50 milligrammes *per centum*.

A number of radiological investigations were carried out. On April 9, in a plain X-ray film of the chest, the lung fields appeared clear. There was some enlargement of the cardiac shadow, the enlargement affecting chiefly the left ventricle. On April 10, in a plain X-ray film of the abdomen, a shadow of a soft-tissue mass was seen in the region of the right kidney. The left kidney shadow appeared normal in position and contour. Excretion pyelography was carried out on April 10. The left kidney was seen to be secreting the solution satisfactorily and there was no definite abnormality on that side. There was no secretion at all on the right side. At a cystoscopic examination on April 11, blood was seen to be issuing from the right ureteric orifice, but urine only from the left. A catheter was inserted into each orifice and the differential kidney function was tested; indigo-carmine was excreted normally on the left side, but none issued from the right. Retrograde pyelography was then performed on the right side (April 12). The tip of the catheter was seen to be lying just above the level of the right transverse process of the fourth lumbar vertebra. There was little evidence of any of the solution proximal to the tip of the catheter, the bulk of it having flowed back into the bladder. There appeared to be a large soft-tissue swelling overlying the lower pole of the kidney, most probably a tumour. Pathological examination of the urine from the left ureter on April 12 revealed two or three leucocytes and five to seven erythrocytes per high power field, some crystals and many

amorphous phosphates ("++"); the urine was sterile. A urea concentration test on April 12 gave a result within normal limits.

Operation was undertaken on April 26. Exposure through Hugh Hampton Young's incision revealed enlargement of the kidney, ureter and suprarenal tissue on the right side, but no obvious tumour mass. The ureter was divided below the enlargement about five inches from the kidney and nephrectomy was carried out. Examination of sections of the kidney revealed almost complete destruction of the

FIGURE I.

parenchyma and pronounced distension of the pelvis and calyces with brownish fluid. Examination of sections of the ureter disclosed a primary tumour causing complete stenosis.

On May 9 a pathological report on material removed at operation was as follows.

The specimen of suprarenal tissue consisted of a small yellowish piece of tissue, which on section was seen to be adrenal gland with cortex and medulla. On microscopic examination the cortex was seen to be atrophic and its cells were unusually foamy. The medulla appeared to be rather more cellular than usual, and at one end of the section hyaline change had occurred in the connective tissue.

The specimen of kidney and ureter consisted of a kidney which had a much dilated pelvis, forming a sac about 11 centimetres in diameter. The kidney itself had much dilated calyces, and the renal tissue was atrophic. In the first part of the ureter there was a very highly villous tumour. The ureter had been opened and the surface of the tumour had been exposed. It formed a mass 5·4 centimetres by 4·0 centimetres in diameter. Microscopic examination of sections of the tumour of the ureter revealed the structure of a carcinoma of a transitional type. Towards one end of the section there were a number of structures which resembled enlarged rete processes, and these were formed of epithelial cells which appeared to be malignant; yet in that part invasion was only just commencing. Further along there was much more tumour growth, and here there was fairly extensive invasion, yet it had not encroached on the muscle, but projected upwards into the lumen, forming a papillary growth. In that part the malignant cells were seen to be small, dark-staining and somewhat spindle-shaped—an appearance typical of carcinomata derived from a transitional type of epithelium. There was no evidence of keratin or of prickle cells.

Convalescence after the nephrectomy and partial ureterectomy was uneventful, and a second operation for removal of the residual part of the ureter was undertaken two weeks later (May 9). The residual ureter was displayed through a lower right paramedian incision. It was dissected down to and through the wall of the bladder, and removed. The aperture thus made in the bladder was sutured and a drain was inserted through the lower end of the abdominal wound. A catheter was passed and left *in situ*. Convalescence was again without complication, except for a transient wound infection. The patient was discharged from hospital on June 19, 1946.

On inquiry from the follow-up clinic, a letter received from the patient on February 6, 1950, stated that he had made a "splendid" recovery, had put on nearly four stone in weight, and was enjoying the best of health.

MONGOLISM IN ONE OF TWINS: REPORT OF TWO CASES.

By BERTRAND A. COOK,
Bulli, New South Wales.

MONGOLISM, that tragic growth disorder of children, has a relative frequency of about three in every thousand births. It is, therefore, a matter of very great importance. However, mongolism in one of twins is very rare, only a total of 81 cases having been reported in world literature up to 1947. The reports in British literature are extremely rare, only three cases being reported in the last twenty-two years—namely, that of Armstrong in 1928, that of Russell in 1933 (both mongoloid), and that of A. R. Graham of Lancaster in March, 1950. In view of the foregoing, therefore, the occurrence of two such cases in one medical practice within the space of five months must be absolutely unique.

Benda (1947) and Brousseau (1928) believe that mongolism is due to hypofunction of the pituitary gland. Benda further has a thesis, along with others, that mongolism usually occurs towards the menopause, or after a period of infertility, during which there may have been miscarriages.

Mrs. K.'s case illustrates this thesis perfectly—that of a woman of thirty-seven years, whose youngest surviving child was aged twelve years; this child had been followed by several miscarriages and then the birth of twins, a boy and a girl, the girl being strikingly mongoloid in appearance. The twins were born on October 17, 1949, after a labour of thirteen hours twenty minutes, the second twin being born five minutes after the first. The labour was perfectly normal; the male twin weighed five pounds one ounce and was 18 inches in length; the mongoloid

female baby weighed four pounds 13 ounces and was 17 inches in length. Both presented by the vertex.

Mrs. B.'s case is somewhat different. She is a woman aged twenty-eight years, of somewhat retarded mental development, but otherwise healthy. Ten years ago I performed a Cæsarean section on her for a *placenta prævia* (central); the result was a live male infant weighing eight pounds, and the convalescence was uneventful. The baby was normal. Since then she has given birth to another normal infant after a normal labour. The twins were born on June 1, 1949. The total duration of labour was two hours fifteen minutes. On account of gross eclamptic toxæmia, the membranes were ruptured to induce labour, which ensued after six hours. The first twin born (vertex presentation) was a female, weighing six pounds nine and a quarter ounces and 19·5 inches in length—a normal infant. The second birth took place fifteen minutes later; the baby was a male, weighing four pounds twelve and a half ounces, and presented by the breech with extended legs. This infant was strikingly mongoloid. In neither case was there a history of German measles during the gestation period.

In harmony with the pituitary and thyreoid hypofunction theories, both infants were treated with thyreoid extract and the appropriate pituitary growth extract. Both children did remarkably well on this line of treatment, supplemented by extra vitamin intake. Though not so bright as their more fortunate twins, both lost a good deal of their mongoloid features. However, a tragedy in the shape of laryngeal diphtheria killed Mrs. B.'s mongol child at the age of nine months. This catastrophe might have been prevented had Mrs. B. been willing to have the child immunized. Mrs. K.'s mongol child continues to improve. Both mothers were confined in Bulli Hospital maternity unit.

Reviews.

THE CYTOLOGY AND LIFE HISTORY OF BACTERIA.

"THE temptation to regard small size and simplicity of structure . . . as criteria of a primitive condition has often proved the cause of error and confusion in the classification of other groups of living organisms. The main reason for the uniform appearance of stained bacteria is that their affinity for the basic dyes commonly employed is so great that the strongly stained cytoplasm and cell membranes mask the underlying structures. The masking effect is accentuated by the shrinkage, often very considerable, reducing the bacterium to as little as half or a third of its natural size." This quotation from the text of A. K. Bisset's "Cytology and Life History of Bacteria" explains its purpose.[1] For many years past Bisset has developed techniques which enable him to study bacteria unaffected by shrinkage, and stained in such a way as to avoid strong basic colours. This is done by fixing living bacteria in the vapour of osmium tetraoxide, hydrolysing them in normal hydrochloric acid at 60° C., and then staining them in a dilute solution of Giemsa stain. A special optical system is employed, and the final magnification in the illustrations is not less than 2300.

The chapter headings speak for themselves. Surface structures, the bacterial nucleus, reproduction, sexuality and life cycles in bacteria are dealt with in turn. Finally the "macroformations", swarming and colony formation are examined. Possibly the most fascinating is the chapter on the bacterial nucleus, which has been postulated, and indeed described several times during the past twenty years. It is now clearly recognizable, and its changes in morphology at different parts of the growth cycle have been established. Suggestive evidence for the existence of a sexual cycle is presented, and this, of course, provokes thought upon the genetic problems of inheritance. If the postulated transference of chromosomal material in the vegetative cycle is true, the wonder is not that bacterial variation occurs so often, but that it occurs so seldom.

It is impossible to criticize constructively such a specialized monograph as this. The laboratory worker using the methods may wish for perhaps a little more detail in the technical sections, but when he assembles the equipment and begins to produce results even broadly comparable with the beautiful illustrations in this book, a new world dawns. It is not too much to prophesy that "Bisset" will become a handbook amongst cytologists, biochemists and physiologists assaulting the secrets of the internal processes of the cell unit.

[1] "The Cytology and Life-History of Bacteria", by K. A. Bisset, Ph.D.; 1950. Edinburgh: E. and S. Livingstone, Limited. 9¾" x 7", pp. 152, with 43 illustrations. Price: 18s. 6d.

UROLOGICAL SURGERY.

THE second edition of Professor Dodson's "Urological Surgery", to which there are twelve other contributors, has been extensively amended and many additions have been made.[1] It is probably the most modern and comprehensive volume in English on urological operations and certainly fulfils the author's objective as "a surgical supplement to the excellent books on the principles and practice of urology".

The main substance of the book is devoted to description of operations—indications, preparation, technique and after treatment. Although the style is lucid and facile, there is most commendable attention to details of anatomy and manipulative methods. This portion is profusely illustrated; hence a rapid and thorough appreciation of the operative procedures is readily acquired. The manipulative aspect of cystoscopy is completely omitted.

No claims are made for originality, but the operations described are those which the author has found useful and are an "expression of his experience". It is rather curious that one of the weakest points is the description of suprapubic prostatectomy which leaves the reader with a confused impression of the author's methods. He does not follow throughout any one of the well-known techniques. The lack of clarity here is quite exceptional, as in some cases as many as five distinct operations are described for the cure of one ailment.

The chapters on diagnosis, urography, radiation therapy, shock and anæsthesia are relatively brief and lacking in detail as compared with those on operations. Outstanding among these, however, is that dealing with acid base and fluid balance which is eminently practical.

The book is well produced on reasonably good paper, clearly printed and adequately indexed, while the illustrations do great credit to both artist and publisher. Typographical errors are unusually numerous.

This is a volume which can be recommended confidently to both specialist and general surgeon, indeed to anyone who requires a *point d'appui* on which to build a sound knowledge of operative urology.

ESSAYS IN PSYCHIATRY.

"PERSPECTIVES IN NEUROPSYCHIATRY" is a volume of essays presented to Professor Golla on the occasion of his seventieth birthday by workers in various fields of neurology and psychiatry, in many of which Professor Golla is himself a pioneer.[2]

Recent work in the anatomy and physiology of the brain is reviewed by Professor Le Gros Clark with special reference to its bearing on the various surgical procedures designed to alter mental functioning. Professor Alfred Meyer discusses the degenerations following pre-frontal leucotomy of which he has made a special study. He suggests that partial or total resection of the prefrontal cortex may be desirable in some cases in which relapse occurs after leucotomy. Dr. Mary Brazier in her chapter on "Neural Nets and the Integration of Behaviour" applies the concept of the "feed-back" to cerebral activity, giving the impression that the brain or parts of it with their "self-propelling" circuits are rather like a perpetual motion machine. The electrocardiograph in psychiatry is the special province of Denis Hill, who tells us that affective illnesses are not yet to be distinguished clearly from

[1] "Urological Surgery", by Austin Ingram Dodson, M.D., F.A.C.S., with many contributors; Second Edition; 1950. St. Louis: The C. V. Mosby Company. Melbourne: W. Ramsay (Surgical) Proprietary, Limited. 9¾" x 7", pp. 860, with 645 illustrations. Price: £7 1s. 9d.

[2] "Perspectives in Neuropsychiatry: Essays Presented to Professor Frederick Lucien Golla by Past Pupils and Associates", edited by Derek Richter, M.A., Ph.D., M.R.C.S.; 1950. London: H. K. Lewis and Company, Limited. 8½" x 5½", pp. 238, with 11 illustrations. Price: 15s.

schizophrenic reactions, although catatonics show a high incidence of electroencephalographic abnormalities of epileptic type. In the process of maturation the prefrontal areas are the last to lose the slow wave activity of under eight cycles per second. Grey Walter discusses the electrocardiograph as an instrument of research in psychiatry and points out that the dominant theme in present-day work is that the brain is an organ for the handling of signals. The editor of the volume, Derek Richter, in "The Biochemistry of Cerebral Function", refers to manic and schizophrenic reactions due to "Atebrin" intoxication. Eliot Slater believes that present tendencies are dysgenic and that to alter this a reorientation of the general attitude towards reproduction will be necessary.

The fifteen contributors have not only honoured Professor Golla, but also have given the world some idea of the researches on various aspects of psychiatry which are being pursued by British workers.

RHEUMATIC DISEASES.

IN the third edition of "The Rheumatic Diseases" by G. D. Kersley, the author has condensed into a small and concise form a general outline of the rheumatic diseases and has included a new short chapter on the latest pertinent advances in endocrinology and histopathology.[1]

In regard to ætiology he suggests that some abnormality in immune body formation, somewhat akin to allergy, is probably a common denominator for all the rheumatic diseases, except osteoarthritis, an hypothesis favoured today by many rheumatologists in the world. The role of the adrenal steroids and "ACTH" in relation to the rheumatic diseases has been considered in brief. Rheumatoid arthritis and Still's disease are treated in an orthodox manner, but the availability of adequate hydrotherapeutic facilities permits a greater emphasis to be made of special therapeutic procedures available at the spa hospital of which the author is chief physician. Aurotherapy in rheumatoid arthritis is still considered as a valuable therapeutic tool, an opinion shared by many. The value of X-ray therapy and the failure of chrysotherapy in ankylosing spondylitis are stressed by the author, an experience common to most rheumatologists. He follows the general rheumatological trend in advocating rest, both physical and mental, combined with movement and regular exercises, as a fundamental therapeutic procedure in the treatment of the rheumatic diseases. The value of hydrotherapy in chronic gout as indicated by the author is probably unknown to many in Australia. No mention is made of Reiter's disease, but the chapter on fibrositis is welcome, especially as many dispute its identity, whilst one on sciatic pain is valuable.

Approximately a quarter of the book is given to special treatment and due emphasis is placed on advantageous therapeutic measures, some of which are the special domain of the spa hospital. It is refreshing to note the constant insistence on focal sepsis as a possible causative factor in many cases of the rheumatic diseases.

This book is suitable for the advanced medical student and general practitioner, and is what it purports to be, an up-to-date outline of the rheumatic diseases and their treatment.

EXAMINATIONS FOR LIFE ASSURANCE.

"THE CONDUCT OF LIFE ASSURANCE EXAMINATIONS", by E. M. Brockbank, now in its third edition, should be in the hands of every practitioner who undertakes the examination of proponents for life assurance.[2] Especially does this apply to general practitioners. As in previous editions, the book contains less than two hundred pages: the author is concise and direct in his approach to the all-important matters of history taking and physical examination and the deductions to be drawn therefrom in assessing the risk. An article is devoted to war experiences and wounds; the author stresses proponent as to receipt of any pension, and if so, the the paramount duty of the examiner to inquire from the relevant facts relating thereto. An interesting discussion is presented on the question of adding a loading to the premium in an impaired life, rather than issuing a policy with reduced benefits for a limited period: this question is very important, and, it is feared, little understood by the general run of medical practitioners. The author's experience leads to the conclusion that only 10% of proponents can be classed as unexceptionable first-class lives. Heredity receives due attention, and it is recommended to ascertain the medical history of the grandparents as completely as possible in this connexion. In this edition new tables are set out dealing with the expectation of life of proponents in whom exists a risk of tuberculosis or cancer. A new and somewhat startling addition contains information showing a correlation between increased smoking, especially in women, and the increase in reported deaths from cancer of the respiratory tract. The sales of tobacco have trebled in thirty years, predominantly in the form of cigarettes, and in the last ten years the deaths from cancer of the larynx, lung, trachea and pleura have increased in varying proportions compared with total cancer deaths, according to official returns of the Registrar-General, and in even greater proportion in the City of Manchester. In the statistical table from the latter the increase amounts to 6% of total cancer deaths. This is a very useful book dealing briefly with all matters relevant to life assurance examination.

[1] "The Rheumatic Diseases", by G. D. Kersley, M.A., M.D. (Cantab.), F.R.C.P. (London), T.D., with a foreword by Sir Francis R. Fraser, M.A., M.D. (Edinburgh), F.R.C.P. (London); Third Edition; 1950. 8" × 5", pp. 164, with illustrations. Price: 15s.

[2] "The Conduct of Life Assurance Examinations", by E. M. Brockbank, M.B.E., M.D., Vict., F.R.C.P.; Third Edition; 1949. London: H. K. Lewis and Company, Limited. 8¼" × 5½", pp. 180. Price: 12s. 6d.

RETROPUBIC PROSTATECTOMY.

COUVELAIRE'S book on the new "retropubic" prostatectomy operation of Terence Millin, of London, is an unusual volume for a medical work, as it is charmingly bound in green cloth with most artistic gold tooling, and the paper and type are of superlative quality and clarity respectively.[1] The text is only short, but is practical and to the point, though a few more important details would have been welcome. Where this monograph scores, however, is by its splendid and large photographic illustrations; although these are sufficiently clear in themselves, aid is given to the understanding of them by the addition of explanatory diagrams.

Many urologists will welcome the action of yet another French urologist in dropping the word "prostatectomy" when no such operation is performed. This word, they hold, should be reserved for the radical operation for carcinoma in which the whole of the prostate gland, as well as the seminal vesicles, is removed. Prostatic adenomectomy is a far better descriptive term, even though it may not be pathologically correct in all cases.

It is a pity that Millin has used the word "retropubic". The word prevesical would have been better, in order to distinguish this operation from the more usual transvesical method, which has commonly been called "suprapubic". Both of these operations are suprapubic in approach and retropubic in execution, so that these terms are not really distinguishing ones.

After describing ligature and incision of the vessels which lie in front of the prostatic mass, the author then states that the incision in the "surgical capsule" should be (*a*) short, (*b*) high and (*c*) bold (meaning deep enough). A transverse incision is usually preferable. One can understand that the incision should be high, since the incised vessels may be difficult to control if too low down; moreover, final closure of the "surgical capsule" is easier and firmer when it is up near the bladder. That the incision should be deep enough is also advisable, so that the true plane of cleavage between adenoma and "surgical capsule" (true prostate) is quickly and surely reached. But one cannot subscribe to a short incision of two to three centimetres; this will surely tear irregularly during the enucleation and extraction of the adenoma.

The steps and method of enucleation are described admirably and every aspirant to the performance of this operation would do well to possess this monograph for the worth of the photographs alone.

A great weakness of the work is the little space and cursory treatment given to the all-important matter of urethral drainage after this operation. Since the era of "closed" adenomectomy began, the surgeon has been dependent on a urethral catheter of some kind to drain the urine (and often clots) during the critical first few days after operation, and much thought on this drainage problem is

[1] "*L'adénomectomie prostatique rétropubienne*", by R. Couvelaire; 1948. Paris: Editions Bernard Baschet. Sydney: W. S. Matsdorf. 10" × 8¼", pp. 106, with many illustrations.

necessary in future; only ten lines are given by this author to this important matter.

No case histories are included in the work; one would have liked a few of them, just to illustrate practical difficulties met during this series.

The author does not give the numbers of the cases on which he bases his work, nor does he analyse them. He states, at the very end, that the number of cases is "over 200", but leaves one with the feeling that others have shared in this total. He does not state his mortality, nor the incidence of the various categories of morbidities, but states obscurely that in competent hands the mortality is about 3%, and that when the operation is done by "several surgeons pooling their statistics" the mortality reaches 10%.

Among causes of death he states that two seem to be peculiar to "retropubic prostatectomy": (i) sudden, unpredictable cardio-vascular collapse, and (ii) abdominal meteorism, with fall of blood pressure, vomiting and paralytic ileus. Nevertheless, in spite of all this vagueness, the author concludes: "the discovery of retropubic adenomectomy has transformed the operative cure of prostatic adenoma".

NEPHRITIS IN CHILDHOOD.

AFTER a preliminary chapter upon classification the greater part of Dr. G. E. M. Scott's brief monograph upon "The Natural History of Bright's Disease"[1] is devoted to a study of a number of cases of acute nephritis in children which failed to resolve within the usual period of hospital treatment. The author has some interesting observations to make, for example, that almost half of these patients exhibited persistent arterial hypertension, whereas only 27% of them had albuminuria, suggesting that urinary findings alone are not a reliable indication of the course of the disease. This work will be a useful contribution to the literature on nephritis.

A TEXT-BOOK OF HISTOLOGY.

FIRST published in 1937, "A Textbook of Histology for Medical Students" by Evelyn E. Hewer has now reached its fifth edition.[2] Dr. Hewer was formerly reader in histology in the University of London and lecturer in physiology at the Royal Free Hospital School of Medicine. Her book is the outcome of nearly thirty years' experience in teaching medical students and is written primarily for them. It follows the usual arrangement of text-books of histology; cells are described first, then tissues, and later, organs. Reference throughout is to human tissue as far as possible. The book concludes with two short chapters on "Certain Abnormal Variations in Minute Structure" and on "Protective Mechanisms in the Body". In an appendix, the simpler methods of preparing tissues for histological examination are outlined. The text is illustrated by 418 photomicrographs and diagrams in black and white. The photomicrographs, many of which are new in this edition, are on the whole excellent. Especially good are the series of photomicrographs of the central nervous system, with their accompanying diagrams; these alone would make this book most valuable to medical students. On the other hand, some of the drawings are extremely poor and so rudimentary as to be of little real use; such, for instance, are the representations of the cells of human blood (Figure 10) and the types of cell found in bone marrow (Figure 16). In the preface to this edition the author writes: "Recent work, including new methods of investigation, provides more information in respect of detail, but the fundamental structure does not alter, and as it was felt desirable that the bulk of the work should not be appreciably increased, such detail has not been included, but some references are given for further study." This may have been a wise and modest decision, but it does place this book at a disadvantage compared with some of the really splendid modern books of histology that are available. On the whole, though this is a good useful text-book, the keen student will want to venture further afield.

[1] "The Natural History of Bright's Disease: A Study from the Standpoint of Pædiatrics", by G. E. M. Scott, M.B. (Melbourne), L.R.C.P. (Edinburgh), L.R.F.P.S. (Glasgow); 1950. Melbourne: W. Ramsay (Surgical) Proprietary, Limited. 8¼" × 5½", pp. 76, with one illustration.

[2] "Textbook of Histology for Medical Students", by Evelyn E. Hewer, D.Sc. (London); Fifth Edition; 1949. London: William Heinemann (Medical Books), Limited. 6½" × 9", pp. 444, with 418 illustrations. Price: 25s.

Books Received.

[The mention of a book in this column does not imply that no review will appear in a subsequent issue.]

"Human Milk: Wartime Studies of Certain Vitamins and Other Constituents", by S. K. Kon and E. H. Mawson; 1950. Medical Research Council of the Privy Council, Special Report Series Number 269. London: His Majesty's Stationery Office. 9¼" × 6", pp. 188, with illustrations. Price: 4s. net.

Based on work extending over four years, the organization of dietary surveys and the analyses of specimens of milk from more than 2000 nursing mothers.

"Children with Mental and Physical Handicaps", by J. E. Wallace Wallin, Ph.D.; 1950. London: Staples Press, Limited. New York: Staples Press, Incorporated. 8½" × 5½", pp. 574, with illustrations. Price: 42s. net.

Intended for non-medical readers.

"The Practice of Medicine", by Jonathan Campbell Meakins, C.B.E., M.D., LL.D., D.Sc.; Fifth Edition; 1950. St. Louis: The C. V. Mosby Company. Melbourne: W. Ramsay (Surgical) Proprietary, Limited. 10" × 6¾", pp. 1578, with 518 illustrations, including 50 in colour. Price: £7 1s. 9d.

The first edition was published and reviewed in this journal in 1936.

"The Mask of Sanity: An Attempt to Clarify Some Issues About the So-Called Psychopathic Personality", by Hervey Cleckley, M.D.; 1950. St. Louis: The C. V. Mosby Company. Melbourne: W. Ramsay (Surgical) Proprietary, Limited. 8¼" × 5½", pp. 560. Price: 68s. 3d.

The purpose of this book is shown in the subtitle.

"Cell Physiology and Pharmacology", by J. F. Danielli, Ph.D. (London and Cambridge), D.Sc.; 1950. New York, Amsterdam, London, Brussels: Elsevier Publishing Company, Incorporated. 9" × 6", pp. 166, with illustrations. Price: 24s.

Based on lectures given at University College, London.

"The Causes of Blindness in England and Wales", by Arnold Sorsby; 1950. Medical Research Council of the Privy Council, Memorandum Number 24. London: His Majesty's Stationery Office. 9¼" × 6", pp. 58. Price: 1s. 6d. net.

A survey based on 19,149 certificates of blindness.

"A Text-Book of X-Ray Diagnosis by British Authors", in four volumes, edited by S. Cochrane Shanks, M.D., F.R.C.P., F.F.R., and Peter Kerley, M.D., F.R.C.P., F.F.R., D.M.R.E.; Second Edition, Volume IV; 1950. London: H. K. Lewis and Company, Limited. 9¼" × 6½", pp. 608, with 553 illustrations. Price: 60s. net.

The first edition was published in 1938-1939.

"Aids to Surgical Anatomy", by J. S. Baxter, M.D., M.Sc., F.R.C.S.I.; Third Edition; 1950. London: Baillière, Tindall and Cox. 6¼" × 4", pp. 212, with 30 illustrations. Price: 5s. net.

One of the "Students' Aids Series". The text has been revised and partly rewritten; a chapter on the autonomic nervous system and certain anatomical and functional principles has been added.

"Aids to Psychiatry", by W. S. Dawson, M.A., D.M., F.R.C.P. (London), F.R.A.C.P., D.P.M.; Sixth Edition; 1950. London: Baillière, Tindall and Cox. 6¼" × 4", pp. 337. Price: 6s. net.

One of the "Students' Aids Series". The text has been revised and chapters on personality and child psychiatry have been added.

"An Introduction to Medical Photography", by Josephine Hunt, S.R.N., S.R.C.N., F.I.B.P., F.R.P.S., with a foreword by Sir Cecil Wakeley, K.B.E., C.B., D.Sc., F.R.C.S., F.R.S.Ed., F.R.P.S.; 1950. London: Staples Press, Limited. New York: Staples Press, Incorporated. 8¼" × 5½", pp. 244, with many illustrations. Price: 30s.

Intended as a practical help to those with some knowledge of photography who are taking up medical photography without previous knowledge of hospitals or medical matters.

The Medical Journal of Australia

SATURDAY, SEPTEMBER 16, 1950.

All articles submitted for publication in this journal should be typed with double or treble spacing. Carbon copies should not be sent. Authors are requested to avoid the use of abbreviations and not to underline either words or phrases.

References to articles and books should be carefully checked. In a reference the following information should be given without abbreviation: surname of author, initials of author, year, full title of article, name of journal without abbreviation, volume, number of first page of the article. If a reference is made to an abstract of a paper, the name of the original journal, together with that of the journal in which the abstract has appeared, should be given with full date in each instance.

Authors who are not accustomed to preparing drawings or photographic prints for reproduction are invited to seek the advice of the Editor.

THE ANNUAL MEETING OF THE BRITISH MEDICAL ASSOCIATION IN SOUTH AFRICA.

In the report of the last meeting of the Federal Council of the British Medical Association in Australia, published in this journal, reference was made to the fact that the Parent Body will hold its annual meeting of 1951 at Johannesburg, South Africa, concurrently with the holding of a meeting of the Medical Association of South Africa. The latter body is affiliated with the British Medical Association and this joint meeting will be of considerable significance. There was a time when the members of the medical profession in South Africa were part of the British Medical Association, but a year or two ago they decided to form a separate association, and to keep the nexus with the Old Country by means of affiliation. This is the kind of bond which binds the Canadian Medical Association and the British Medical Association. Members of the medical profession in Australia will recall the stimulus and inspiration which they received when the British Medical Association held its annual meeting at Melbourne in 1935. Neither can they fail to remember the great impression created throughout the country by the spectacle of an enormous delegation (more than 270 persons) who travelled across the world from the United Kingdom and other parts of the Empire to attend the meeting. South Africa will next year receive the same kind of stimulus and inspiration and will enjoy the same kind of spectacle. It is most appropriate that the united meeting in Johannesburg will be preceded by a session of the British Commonwealth Medical Conference—the fourth in the series, if the inaugural meeting in London is included. In the present troubled state of the world, when doubt is in the minds of many people and suspicion is easily aroused, every Branch of the British Medical Association, wherever it is situated, and the whole affiliated Canadian Medical Association should do everything possible to make of the South African meeting a memorable event.

The meeting will be held on July 16 to 21, 1951, at the University of the Witwatersrand, Johannesburg, under the presidency of Dr. A. W. S. Sichel, President of the Medical Association of South Africa. Dr. H. Moross is general secretary, Dr. C. C. P. Anning is organizing secretary and Dr. R. Geerling, medical secretary. The chairman of the Organizing Committee is Dr. A. J. Orenstein, who visited Australia recently to attend the third International Conference of Experts on Pneumoconiosis. The scientific sections of the meeting will number twenty-one, and thus all scientific interests should be met. On the social side it is intended that tours shall be arranged to such famous places as the Kruger National Park and the Victoria Falls. Notice of the meeting is given at this early stage for the reason that Australian practitioners intending to travel abroad have to make their plans well in advance. Those who are travelling to or returning from the United Kingdom would find much to interest them at the meeting and in addition would have an opportunity of seeing something of a country teeming with historical and racial interest and full of attraction to the tourist. The Federal Council will be represented at the meeting, in all probability by one of its members. Others who can attend will have a unique experience and will also do something to cement the bonds between the different parts of the British Commonwealth. Dr. A. H. Tonkin, who represented South Africa at the recent British Commonwealth Medical Conference at Brisbane, and Dr. Orenstein extended cordial invitations to Australian members of the British Medical Association and assured them of a warm welcome.

THE EMPIRE MEDICAL ADVISORY BUREAU: THE NEED FOR A CONDITIONED REFLEX.

Members of the Australian Branches of the British Medical Association who have visited England during the last few years have been helped in many ways by the Empire Medical Advisory Bureau which was set up late in 1947 by the Parent Body at British Medical Association House in Tavistock Square. Its objects were set out in a leading article in this journal on July 3, 1948. As stated on that occasion, one of the main objects of the Bureau is to welcome overseas visitors from the Dominions and to make them feel at home in England. Many Australians visiting the United Kingdom for the first time feel the need of someone to whom they can go for reliable and friendly advice. This bureau is such a place. Dr. H. A. Sandiford, the Director, and his staff can give detailed information on facilities for post-graduate studies, and when required will be able to provide the visitor with introductions. The Bureau will also, if need be, help visiting graduates to find suitable lodgings. Here again reference may be made to London House and its facilities. Members of the Branches who see a statement about the existence of the Empire Medical Advisory Bureau and what it is able to do may take little notice of what they read and when they arrange to visit the Old Country forget what they have read. What we should like to see developed is a kind of conditioned reflex so that when a journey abroad for post-graduate study is mentioned, both the traveller and his friends will at once call to mind the bureau which the British Medical Association has provided.

Current Comment.

VASCULAR SURGERY AND INERT VASCULAR TUBES.

RESENTFUL NATURE has her own defence against the introduction of substitute materials by the surgeon, though the persistence of experimenters begins to wear that resistance down. Improved knowledge and technique have made the use of grafts safer in vascular surgical work, and trials of inert substances have been meeting with more success. Tissue grafts have obvious advantages and also obvious drawbacks. In plastic surgery, for example, it is troublesome to meet with the complication of infection in the donor site of an iliac graft. In vascular repairs the responsibility is much greater, and risks must be very carefully weighed. Recent studies have been made by Thomas J. Donovan and Bernard Zimmermann on the effect of artificial surfaces on blood coagulability.[1] While examining the behaviour of several substances they paid particular attention to polyethylene, a plastic made by polymerizing ethylene under heat and pressure to chains of hydrocarbons longer than those of paraffin. By analogy with other synthetic structures of simple type this substance might be expected to behave favourably in the body tissues, that is, to produce a minimal reaction. Previous researches have shown that pieces of polyethylene can be buried in the cerebral cortex of experimental animals for long periods without any but a slight glial reaction. It has been found that this applies only to the pure product, as the substance made commercially as an insulator contains irritants. The blood coagulation time and the capillary action in polyethylene tubes were studied by Donovan and Zimmermann and comparison was made with tubes of glass, paraffin and collodion. Pieces of the polyethylene were buried in the backs of rats for various intervals and the reactions were compared with those caused by lucite, another plastic tolerated well by animal tissues. Only slight fibrotic reaction was observed. Blood obtained by venepuncture was introduced into tubes of polyethylene and of glass lined with films of collodion and paraffin and the coagulation times were noted by the appearance of the first trace of fibrin precipitate. To measure the surface action, tubes of glass and polyethylene were compared with regard to their capacity to attract or repel water. Plasma was also investigated, but the very low values obtained were chiefly useful in ensuring that the readings for water were valid. The polyethylene tubes took a period of days to attain such a degree of "wettability" as to ensure an accurate capillary reading. To obviate this, polyethylene tubes were immersed in water for periods of up to two months. These experiments showed that the clotting time in polyethylene tubes was about twice that in glass, and nearly as long in tubes lined with collodion and paraffin. In this it resembles lucite. Clot retraction was moderate and similar in all, except in the collodion tubes, in which it was absent. The capillary investigations showed that polyethylene first repels water, and then after some days gradually attracts it. The point of this finding is that the effect of a surface in delaying the clotting of blood is proportioned to its capacity to repel water. It will be noted that this type of research can be of everyday importance, affecting for instance the materials used in blood transfusion apparatus. There is already a considerable literature on this particular subject, and it is likely that this will be expanded by work on the chemistry of synthetic plastic substances, and the necessary biochemical and biophysical experiments which link basic and applied research to clinical requirements. Frances E. Horan, F. G. Hirsch, L. A. Wood and I. S. Wright, in an account of an inquiry into surface potentials of materials in relation to blood clotting, remark that such work is no longer a laboratory curiosity but of practical clinical importance today.[2] They further point out that much remains to be done in this field, as it is conceivable that the function of anticoagulants may be partly of an electrical nature. They have examined in this work the surface potentials using various solutions in vitreous silica and silicone-coated capillary tubes. Further details of the surface or zeta potential in relation to blood and blood components and to anticoagulants would lead us too far afield. At the present it is sufficient to indicate that technical workers are not so remote from the bedside as they sometimes appear.

[1] *Blood*, December, 1949.

[2] *The Journal of Clinical Investigation*, February, 1950.

THE DIAGNOSIS OF AORTIC LESIONS.

THE great advances in diagnosis and treatment of congenital cardiac lesions, and the application of angiocardiography and cardiac catheterization with its intimate associated studies of respiratory chemistry, have perhaps diverted attention from some of the serious forms of aortic disease. When visceral syphilis was fairly common, syphilitic aortitis was of considerable clinical and radiological interest, and the attention rightly paid to coronary occlusion resulted in the collection of numbers of cases of dissecting aneurysm of the aorta, owing to certain clinical resemblances in the emergent symptoms caused by both conditions. References have been made in these pages to the latter lesion, and W. F. Emery published a series in this journal in 1946.

In spite of the recent advances in the treatment of syphilis, only time and experience can show how common or otherwise will the visceral complications be in the future, but it is surely safe to predict that treponemal aortitis will still be seen occasionally. It has always been recognized as a serious condition, and its diagnosis is therefore important. G. E. Peabody, G. C. Reader, C. T. Dotter, I. Sternberg and B. Webster have published a study of the value of angiocardiography in the diagnosis of cardio-vascular syphilis.[1] They have recorded their findings in the examination of 93 patients in the New York Hospital, and compare the merits of physical signs, routine radiography of the thorax and angiography. From films taken with the contrast medium the contour of the aorta was clearly seen in the left anterior projection, and by comparison with a control series of 100 normal aortas a standard cross-section was established as 38 millimetres. This standard actually included measurements of individuals with atherosclerosis, so that the authors regard this figure as representing the maximum calibre of the mid-ascending aorta in non-syphilitic persons. The changes which they considered to be characteristic of syphilitic aortitis were dilatation beyond the limit of 38 millimetres, irregularity of the aortic wall, and variations in its thickness, calcification and tortuosity. Individual signs in this list may, of course, be found in other pathological conditions, but the authors believe that the whole complex is of great diagnostic significance. Of 83 patients with late syphilis, and therefore candidates for specific aortitis, 49 were found to have cardio-vascular syphilis, with signs of aortitis, aneurysm or valvular insufficiency; in 34 of these cases the diagnosis could be made in the usual way, by clinical examination and plain X-ray examination of the chest, but in the remaining 15 the condition was revealed only by angiography. The authors point out that early diagnosis is not always possible, and in the past it has often happened that rapidly lethal aortic disease was present before the diagnosis was established. They therefore claim that this special method has an important application in the investigation of patients with late syphilis.

The other aortic condition mentioned above, dissecting aneurysm, has had the reputation of being almost always discovered after death. Shennan, in a well-known review of the subject, collected 317 cases, but in this series up to 1933 only six cases, that is, 1·8%, were correctly diagnosed during life. Since more attention was directed to this

[1] *The American Journal of the Medical Sciences*, March, 1950.

serious emergency, for it is by rupture or leakage that the lesion usually advertises itself, the percentage of successful diagnoses seems to be rising. David C. Levinson, Donald T. Edmeades and George C. Griffith have found some 734 cases of dissecting aneurysm in the recent literature, and in 88 of these, 10·6%, a diagnosis was made during life.[1] A possible corollary of this is that survival after a vascular episode might occur, and this, too, is recorded by these authors, who state that of their own series of 58 patients, 21 died within forty-eight hours of the onset of symptoms, 22 survived for three to sixty days, and 15 survived for three months to eight years. The percentage in which healing was considered to have taken place varies from 10 to 25 with different authors.

The factors in diagnosis are stated in the article of Levinson and his colleagues as follows. The history usually points to preexisting arterial hypertension. The onset of symptoms is dramatic as a rule, though in the subacute variety the onset may be much more gradual. Pain is usually very severe, causing extreme distress and shock. It radiates to the abdomen frequently, and its centre may often be in the epigastrium, a localization which is of diagnostic importance when present. So, too, is radiation of pain to the extremities when it is present. Interruption of the cerebral blood supply may cause varied symptoms, such as syncope, loss of consciousness, weakness and loss of sensation in one extremity or more, and even hemiplegia. Aortic diastolic murmurs in association with aneurysmal dilatation of the aorta are of high diagnostic importance, and if serological tests show no evidence of syphilitic infection, the probability is that this is a dissecting aneurysm. Other features which may help are inequalities of blood pressure, renal symptoms, such as oliguria, hæmaturia and pain in the flank, elevation of the icteric index and of the serum amylase content. Radiological examination is, of course, of the greatest value; the heart may merely show some enlargement, but the supracardiac shadow is usually widened and the aorta is progressively enlarged, with sometimes a "double-barrelled" shadow. Pleural effusion is relatively common, and the fluid may be blood stained. The authors found no special features in the electrocardiogram, but, as might be expected, normal tracings are an unlikely finding in patients with dissecting aneurysm. Their article quotes illustrative cases in which the correlation between the clinical story and the pathological findings is made, and a good review of the literature is given. It would seem that whatever may be the chance that syphilitic disease of the aorta may become rare, the clinician will still have to consider other forms of disease of the large arteries in the production of medical emergencies.

KEROSENE POISONING.

KEROSENE POISONING is not a common occurrence nowadays, but occasionally small children are involved. It is generally regarded as a problem almost exclusively of rural areas, but shortages of electricity, gas and coke have brought it back, potentially at least, to the urban household, and the family doctor needs to know how to cope with it when it arises. It is, for fairly obvious olfactory and gustatory reasons, a problem mainly of very young children. In a series of 25 children who had ingested kerosene, studied by E. S. Reed, S. Leikin and H. D. Kerman,[2] the ages of the patients ranged from ten to thirty-six months, with an average of sixteen months. They were mostly regarded as being of a mischievous nature and parental supervision was often lax. The most commonly observed symptoms were those of irritation of the respiratory tract—coughing and choking—followed, in order of frequency, by fever, vomiting and lethargy. No definite correlation was found between vomiting or gastric lavage and the occurrence of pulmonary radiological changes that might have given an indication of the frequency of aspiration among patients who vomited or were subjected to lavage. Only one patient had abdominal pain and convulsions. Eight of the 25 children had clinical evidence of pneumonia, and of 22 studied radiologically 19 had pulmonary changes. The onset of symptoms was abrupt and occurred immediately after the ingestion of the material. This fact and the appearance and rapidity of development of the radiological changes indicate, according to Reed, Leikin and Kerman, that the primary acute pulmonary change is one of pulmonary hyperæmia and œdema. Treatment is a matter for considerable discretion. Because of the important pulmonary changes, Reed, Leikin and Kerman emphasize the importance of oxygen in the treatment of these patients. Even though no definite evidence was found that gastric lavage or vomiting was related to the incidence of pulmonary affection, they feel that lavage is contraindicated except when large amounts of kerosene have been ingested, and then should be used only when reasonable care is taken to prevent aspiration. Administration of emetics should also be discouraged because of the probability of aspiration on the part of younger children. Antibiotics may be used on a prophylactic basis to prevent or alleviate secondary bronchopneumonia, pulmonary abscess and the like. Other symptomatic and supportive measures should be used when indicated.

The emphasis of Reed, Leikin and Kerman against lavage is rather a departure from the treatment of kerosene poisoning generally advocated. As a rule lavage has been laid down as the main immediate measure, especially if ingestion has been very recent, although the dangers of aspiration are recognized. It was pointed out by Harry Gold, at a conference on household poisonings at Cornell University Medical College,[1] that it is not certain how the lungs become involved, whether by excretion of the volatile agent through the lungs or by aspiration during vomiting. In animal experiments the fatal dose when kerosene is given by the stomach is about ten times that when it is given by intratracheal injection; this may indicate rapid absorption from the pulmonary bed or severe inflammatory reactions to the high concentration. In any case it seems reasonable to empty the stomach as quickly as possible if it is likely to contain any appreciable quantity of kerosene, but at the same time the cautious attitude of Reed, Leikin and Kerman should be borne in mind. These two points of view are something like opposite phases of the swing of a pendulum. The resting point remains to be found.

[1] *Circulation*, March, 1950.
[2] *American Journal of Diseases of Children*, April, 1950.

INFANT AND CHILD FEEDING.

THE Council on Foods and Nutrition of the American Medical Association has been publishing a series of articles which it is intended will appear in the near future in book form as the Council's "Handbook of Nutrition". The article on the feeding of healthy infants and children, which has been prepared at the request of the Council by Philip C. Jeans,[2] is thoughtful and informative and should be of general interest. Jeans considers that, despite all our modern knowledge of infant nutrition and all the current refinements of artificial feeding, feeding at the breast of the mother remains an ideal procedure. This is true, although human milk contains only a bare minimum of most of the nutrition essentials and although the body composition of the breast-fed baby departs widely from that which preceded and that which follows, in contrast to the body composition of the artificially fed baby, which maintains more closely a smooth continuance of the fœtal and post-infancy curves. Jeans has a good deal to say

[1] *The American Journal of Medicine*, February, 1949.
[2] *The Journal of the American Medical Association*, March 18, 1950.

on vitamin requirements. Vitamin *D*, he states, is needed early by all babies, whether breast or artificially fed. Vitamin *C* is needed early by artificially fed babies and is a harmless safeguard for the breast-fed baby; babies born prematurely have a need for vitamin *C* somewhat greater than that of babies born at term, and this need exists from the time of birth. No need exists for vitamin *A* from special sources. Jeans considers that if current custom is in error in these matters, it errs in the direction of giving too much vitamin *D* and too little vitamin *C* and in not giving either of these early enough. Additional supplementary foods should be given at not later than four months of age, one important function of supplements being to supply iron and vitamins of the *B* group. Another function is to accustom the baby early to variety in flavour and texture for the promotion of good feeding habits; anorexia and poor feeding habits, which occur so frequently in older children, often have their origin, Jeans believes, in feeding mismanagement in infancy. He then goes on to discuss the feeding of children after the period of infancy. He considers that in a general way we have done reasonably well nutritionally for our babies, but not so well for children past infancy. The nutrition of the child has been improved during the past generation, but not to the extent desirable or possible with present knowledge. More can be done in the field of dental caries, which appears to be a nutritional problem. Although observers do not agree fully on the particular nutritional or dietary factors responsible for dental caries, nearly all believe that one or more dietary components may be responsible, because of either lack of those that are essential or the presence of some considered harmful. Jeans calls attention to three nutritional essentials which deserve special emphasis in childhood, namely, vitamin *D*, protein and calcium. Vitamin *D* is required throughout the growth period, a fact widely overlooked. Milk as the only constant good food source of calcium is not taken in sufficient quantity by a large number of children. Protein deficiency is much more common than is generally realized; a diet adequate in protein cannot be arranged fortuitously without the inclusion of milk. Thiamine intake is a matter of some importance. Jeans points out that although thiamine is obtained by a large proportion of children in quantities scarcely meeting their needs, the remedy lies in better food selection, not in thiamine medication. Enrichment of flour and bread has contributed materially to the desired end; decreased consumption of sugar also should be helpful. The position is different with vitamin *A*; its supply from special sources is not needed by the normal child. If a diet is fortuitously deficient in vitamin *A*, it is deficient also in other respects. The remedy is a better diet, not medication. With the wealth of data and considered opinion available in such articles as this of Jeans there is little valid reason why a better diet should not be generally adopted for infants and children.

THE CAROTID SINUS SYNDROME.

FOURTEEN years ago one of the early articles, perhaps the best known article, on the hypersensitive carotid sinus was published by S. Weiss, R. B. Capps and E. B. Ferris. Since then many contributions have been made on this subject, and Arthur J. Draper has just published another in which 11 cases are described with relevant comments.[1] The name of Hering is well known, too, from the physiological aspect, and in his original paper in 1927 he also referred to the clinical phenomena. Weiss and his colleagues emphasized the variety of the stimuli which could initiate the uncomfortable symptoms produced by excitation of a hypersensitive carotid sinus, and amongst these mentioned such simple procedures as turning the head, posturing during the act of shaving and wearing a tight collar. Other writers have not found such alleged excitants to be of frequent importance, and Draper states that in an analysis of 59 cases described in the last ten years a precipitating factor could be found in only 18. The diagnosis of this condition is not entirely free from risk, for it cannot be made with certainty unless symptomatic changes and an alteration in the rate of the heart are produced by mechanical stimulation of the sinus, which if too prolonged could cause dangerous syncope. One sinus only should be subjected to pressure at the one time, and the test should be applied to the patient in the sitting posture. The "vagal" syncope which may sometimes be thus produced is now more cautiously called "cardio-inhibitory", but syncope is not necessary for a diagnosis, for, as Weiss and others pointed out, fall of blood pressure or loss of consciousness without demonstrable change in the circulation may also be observed. Other writers think that temporary slowing or disturbance of the cardiac rhythm or brief standstill is the most convincing diagnostic finding on the application of pressure to the sinus. The wider use of the electrocardiograph has added to the precision of observation. Draper has assembled from the literature and his own observations a number of contributory factors in the occurrence of this syndrome. Most of the subjects are males, and usually of the higher age groups. Local vascular changes have been described, but these rest on an insecure basis. Whether there is any connexion between this syndrome and the occurrence of anginal symptoms has been debated; the answer is probably given on the observation that half the patients reported have had evidence of arteriosclerotic or hypertensive vascular disease. Electroencephalographic studies have not been of practical assistance. Clinical studies have been more illuminating, though the older the patients are, the more prone they are to suffer from concomitant cardio-vascular disease, which tends to be confusing. The symptoms varied considerably in Draper's younger patients; some of the manifestations were disarming, but others were most disturbing and sometimes dangerous. The most interesting feature of the attacks was that they all presented in one form or another syncope of a puzzling type. Draper was able to demonstrate a response of some kind in varying degree to stimulation of the carotid sinus in all his patients. Sudden change in posture was found effective in a number. Treatment of this condition includes the use of ephedrine and belladonna. In this series extract of belladonna was used with success. The author admits that specific results cannot be claimed, but at least no further syncopal attacks occurred in any patient. Phenobarbital was used in addition according to indications. This syndrome is occasionally seen; perhaps it is more common than the literature would suggest.

[1] *Annals of Internal Medicine*, April, 1950.

THE END RESULTS OF PENICILLIN THERAPY IN SUBACUTE BACTERIAL ENDOCARDITIS.

NOT long ago when no effective treatment was known for bacterial endocarditis, the opinion was sometimes expressed that even if the local infection in the heart valves or neighbouring endocardium could be overcome, the heart could not for long survive the malign effects of damage already inflicted. It is now time to inquire how sustained have been the benefits conferred by penicillin upon this once almost invariably lethal disease. It is five years since penicillin was first successfully used in the treatment of subacute bacterial endocarditis, and the number of studies of survival rates is increasing. As might be expected, deaths have occurred from cardiac failure, renal failure, and local lesions in the heart such as aneurysms. P. L. Pillsbury and M. J. Fiese have published a series of thirty-one reports on patients whose after-histories have been reviewed.[1] They quote other writers' findings, which show considerable numbers of deaths from cardiac failure, reaching nearly one-third of

[1] *Archives of Internal Medicine*, April, 1950.

the total number of patients treated. Renal complications have been less common, though a definite number of patients have had uræmic sequels, and others, embolic accidents. One of the predicted results, that patients with deformed architecture of the heart valves would be more likely to suffer reinfection from external infections, has been hard to assess. Not many recurrent or externally derived infections seem to have been seen, though the finding *post mortem* of viable bacteria embedded in the valvular tissue introduces another possible factor. Pillsbury and Fiese base their own observations on a series of 31 patients who were treated in one hospital between 1944 and 1946. There were 23 males and eight females in this group. With the exception of one patient who died shortly after beginning treatment, the others have been followed at least up to 1948 or until death, and 13 were recently admitted to hospital for the special purpose of investigation for this study. Ten patients died in all. Investigations in hospital comprised blood count, estimations of the blood sedimentation rate, the taking of the Addis count, estimation of the venous pressure, estimation of the circulation time, and radiological and electrocardiographic examinations. The general results showed that one-third of the patients died, eight from cardiac failure, and two from other causes after the cardiac condition had become stationary. Two patients showed evidence of recrudescence of infection, but were successfully treated with further exhibition of penicillin. It is interesting that embolic phenomena were observed frequently after the completion of a successful course of treatment. Most of these were minor in nature, such as petechiæ, and small bleedings under the nails, and though they occasionally persisted for months they were not necessarily of evil significance. Even major embolic events, such as those occurring in the central nervous system, did not preclude recovery. The prognosis with regard to the function of the kidneys is a matter of great interest and importance, seeing how common is the "flea-bitten" kidney, and how often evidences of renal involvement occur during the florid disease. Though deaths have occurred from renal disease in other series, these authors did not find any significant disturbance of renal function in their recovered patients. Thirteen out of the 31 patients had no complications of any kind after treatment, cardiac compensation was well established, and the use of penicillin was an unqualified success. A few abnormalities were found in electrocardiograms, such as auricular fibrillation, and X-ray examination occasionally showed variable but not considerable enlargement of the transverse diameter of the heart. Only eight of the survivors failed to show any substantial evidence of cardiac damage, but on the whole the end results are encouraging. This series shows that even the presence of disturbing signs during treatment, such as embolism, may not warrant pessimism, and perhaps the risk of recurrence of infection may be less than once we feared. Treatment of subacute bacterial endocarditis with penicillin is well worth while, though miracles must not be expected.

THE NEW INTERNATIONAL LIST OF THE CAUSES OF DEATH.

THE possibilities of obtaining information of scientific and administrative value from a study of the causes of death as shown in official statistics were first clearly appreciated by John Graunt, who studied the now famous Bills of Mortality of the city of London just before the Great Fire. England and Wales in the early part of the nineteenth century adopted a system of registration of death by cause and sex and age. William Farr showed what important conclusions could be derived from such statistics. He was anxious, moreover, that comparisons should be available on a world-wide basis and that the classifications of mortality and of morbidity should be reconciled. It may be said with the appearance of the new manual on the "International Statistical Classification" prepared by the World Health Organization that his hopes have been fulfilled.[1]

Diseases and injuries are classified into some thousand main headings or rubrics, and so arranged that diseases of a like nature can readily be grouped. Further subdivisions are also provided for, if desired for any special purpose. The comparability of international statistics will be enhanced by the publication of an index in the manual.

The new classification has made a break with recent traditions in another way. For many years, it had been customary to code the cause of death according to arbitrary rules of preference in those cases in which more than one cause of death was shown on the certificate. In many cases this led to the classification of the death in a category that would be regarded by most medical persons as unsatisfactory. Thus if a patient died in diabetic coma and if tuberculosis was mentioned as a contributory factor, then the death would be coded to tuberculosis. Dr. Percy Stocks,[2] Chief Medical Statistician to the General Register Office, experimented over a number of years with a system whereby the opinion of the medical officer certifying was sought as to the cause underlying the events leading up to death. His ideas have been incorporated in the new classification and index. A uniform type of certificate is to be adopted in all the member States of the World Health Organization. This is the English form, familiar to medical officers in the Australian States, consisting of two parts. In Part I the certifying officer is encouraged to put the causes that led up to death in such a way that the most fundamental is on the last line, that he fills in, of this part. If there are additional causes that are not in this direct line of causes, the certifying officer may put them in Part II of the certificate. However, if the cause of death is given, for example, lobar pneumonia, then there is no need to specify the mode of death such as circulatory collapse since it is the fundamental cause that initiated the train of events leading to death that is required. Additional lesions may be noted in Part II if desired, but if any cause is part of the train of events then it should be retained in Part I of the certificate. The physician should always consider whether a single cause will adequately describe the cause of death.

Some points may be made as to new problems arising from the new system. Firstly it will be essential to have the cooperation of the medical officers, and secondly it will be necessary to ask for more detailed remarks on some of the certificates that have not been filled in fully. A very common practice in Australia is to assume that "hemiplegia" not otherwise specified is to be taken as "cerebral hemiplegia". But the statistician is not allowed to make this assumption, and unless he asks the medical officer whether the condition was cerebral and what was its cause, the death must be assigned to a category that contains rather vague terms, which is undesirable. So that it appears that it will be necessary for the statistician to adopt some system of inquiries. This will have the effect of clarifying the particular case and of making clear the precise information required on the certificate. It also appears desirable that there should be set up in Australia a committee which will facilitate such cooperation between the statistical offices and the profession. In other countries, England and Wales, Canada and the United States of America there are such committees and their opinions have helped to form the present classification.

[1] "Manual of the International Statistical Classification of Diseases, Injuries, and Causes of Death: Sixth Revision of the International Lists of Diseases and Causes of Death Adopted 1948"; 1949. Geneva, Switzerland: World Health Organization. London: His Majesty's Stationery Office. 9½" x 6¼". In two volumes. Volume I, pp. 416; Volume II, Alphabetical Index, pp. 552. Price: 30s.

[2] *British Medical Journal*, May 6, 1950, page 1044.

Abstracts from Medical Literature.

PÆDIATRICS.

"Phenurone" in Epilepsy.

SAMUEL LIVINGSTON AND LASLO KAJDI (*The Journal of Pediatrics*, February, 1950) describe the treatment of a series of 104 epileptics with "Phenurone". In 73 cases the epilepsy was idiopathic, and in 31 it was organic. The type of fit was *grand mal* in 19 cases, *petit mal* in 18, psychomotor in 46, and a combination of *grand mal* and *petit mal* in 21. More than half the patients had proved resistant to treatment with other drugs. The dose given was 0·25 gramme to 1·0 gramme three times daily to children under six years and twice this to older children. In 40% of cases control or great improvement occurred, the best results being with psychomotor seizures and the worst with *petit mal*. Toxic reactions sometimes occurred and necessitated withdrawal of the drug; these included personality changes, skin rashes, proteinuria, drowsiness, headache and hepatitis. The personality changes were marked overactivity, restlessness, insomnia, and constant and often incoherent conversation. In each case the toxic symptoms disappeared on withdrawal of the drug. "Phenurone" is phenacetylurea and is chemically related to "Dilantin" and "Mesantoin".

Congenital Myasthenia in Siblings.

PAUL M. LEVIN (*Archives of Neurology and Psychiatry*, December, 1949) describes two cases of congenital *myasthenia gravis*. He states that in these cases the muscles supplied by the cranial nerves are the ones most severely involved. Diagnosis can be difficult, because the lesion is frequently symmetrical, the condition is stationary in its course, and the limited activities of a child mask the muscular involvement.

Thoracic Surgery in Pædiatrics.

MAURICE G. BUCKLES (*The Journal of Pediatrics*, May, 1950) reviews the recent advances in the more common conditions of the thorax that can now be treated surgically. He emphasizes the importance of adequate pre-operative and post-operative care by the use of chemotherapy, adequate fluid balance and tracheal and bronchoscopic aspiration. He states that benign œsophageal obstruction due to cicatricial stenosis is treated by bougie dilatation when possible, but a number of successful cases of resection of short strictures have been reported. With congenital atresia of the œsophagus, in the majority of cases a blind upper pouch exists, and the lower segment connects to bronchus or trachea by a fistula. Occasionally the upper segment of the œsophagus connects with the respiratory passages, but both or neither may do so. Early surgery is essential, before inhalation of regurgitated food has caused pneumonia. Two fairly large series of cases are referred to, each with a successful survival rate of about 50%. Diaphragmatic hernia may be repaired with a transthoracic or abdominal approach, the former tending to give better results. Mediastinal tumours are uncommon, and precise diagnosis of their nature is often impossible without biopsy. They are often malignant and inoperable, but unless pre-operative evidence of this is available, exploration is worth while. Cystic disease of the lung may be symptomless, or may cause symptoms due to pressure, infection or rupture. Removal of the cyst is indicated when symptoms are present and the individuals are fit for operation. Lung abscess presents a difficult problem. The treatment of an acute abscess should be medical by means of antibiotics and postural and bronchoscopic drainage; but surgical removal of the involved lung tissue should be carried out as soon as any unsatisfactory turn in the response to medical treatment occurs. The results of surgical treatment of chronic lung abscess are not good, and the early surgical intervention is wise. Bronchiectasis is a very common and serious disease. In a series of 400 cases reported by Perry and King the mortality rate was 26% over a period of twelve years among the patients treated non-surgically. Strieder is reported to have produced evidence that children who develop bronchiectasis before the age of ten years do not live beyond the age of forty years. Surgical results are good. Children stand lobectomy well, and even pneumonectomy or bilateral lobectomy. Cure or great improvement is achieved with suitable operative measures.

Tetanus Neonatorum.

D. B. JELLIFFE (*Archives of Disease in Childhood*, June, 1950) describes a series of 25 cases of *tetanus neonatorum* occurring in Nigeria. They occurred in babies born in native homes in a large town, where goats wander in and out of the houses, and the whole town is covered in dust in the dry season. The cord is cut at birth with a sharp palm splinter or piece of broken bottle and a crude dressing applied. The incubation period varied from five to ten days. In every case the earliest feature noted by the mother was the child's inability to suck the breast, followed after about twenty-four hours by increasingly frequent extensor spasms. Constipation and continual crying were common. In the resting posture the child had a moderate *risus sardonicus* with the eyes held closed, slight hyperextension of the spine, the arms semiflexed at the elbows, the hands clenched, and the legs semiflexed at the knees. Tetanic spasms were superimposed on this background. These produced a considerable increase in the hypertonus seen in the resting posture, and also spasm and rigidity of the muscles of the anterior abdominal wall, adductor spasm of the thighs, dorsiflexion of the feet, and severe plantar flexion of the toes. Spasms occurred every few minutes. The umbilicus was clinically infected in most cases, a black eschar being common. Antitetanus serum, 20,000 units, was given by intramuscular injection in all cases. Expressed breast milk was given by spoon or pipette. Subcutaneous saline therapy was needed in most cases. An attempt was made to nurse the babies in a quiet corner of the ward, but often the mothers insisted on carrying the babies about on their backs. Sedation with intramuscular injections of paraldehyde, two to four millilitres each four hours, greatly decreased the frequency of spasms. Oral or rectal administration of chloral hydrate was sometimes used as an alternative. On two occasions the injection of paraldehyde caused chemical abscesses of the buttocks. This treatment was limited by the drugs available, and the results were very bad. One patient survived, one lived for forty-two days, six lived for three to five days, and seventeen died in the first thirty-six hours of treatment.

Intelligence Quotient after Erythroblastosis Fœtalis.

JOAN M. GERVEN AND RICHARD DAY (*The Journal of Pediatrics*, March, 1950) have assessed the intelligence quotient of 68 children who had recovered from *erythroblastosis fœtalis* without suffering any apparent motor-nerve damage. They state that in the group with obvious motor-nerve damage intelligence also is often seriously impaired. It has been claimed by Yannet that in a group of mentally deficient children, significantly more children than expected were Rh-positive and had Rh-negative mothers, and he suggested that such incompatibility might be a not uncommon cause of mental deficiency without motor disability. Children who suffer from kernicterus form a very varied group, but this follow-up investigation was carried out on children who had not been suspected of having brain damage. Siblings were used as a group for comparison. With the Stanford-Binet scale the average intelligence of these 68 children was found to be lower than that of their unaffected, older brother or sister. Statistical analysis shows that the inferiority is not likely to have resulted from chance or from the circumstance that the affected child was always younger than his unaffected sibling. The extent of the impairment is slight, the mean difference in intelligence quotient being only 11·8, so that there is no occasion for altering the usual custom of giving a good prognosis to the parents of a child who has recovered from *erythroblastosis fœtalis* without obvious motor-nerve damage.

Pseudohypoparathyreoid Tetany.

H. BAKWIN *et alii* (*The Journal of Pediatrics*, May, 1950) reviews the subject of pseudohypoparathyreoidism and reports a case. He states that this rare error of calcium metabolism is thought by Albright to be due to an insensitivity of the receptors to parahormone. The patients have low blood calcium and high blood phosphorus levels with a normal plasma alkaline phosphatase level, but they fail to respond to injections of parahormone by a rise in blood calcium level and an increase in urinary excretion of phosphorus as do normal individuals and patients with true hypoparathyreoidism. The clinical picture of pseudohypoparathyreoidism is distinctive, having the following features: *symptoms and signs of tetany*—convulsions, carpo-pedal spasm, laryngeal spasm and positive Chvostek and Trousseau signs; *changes in body configuration* suggestive of, but not typical of, achondroplasia—short stature, sturdy build, rounded features and irregularities in the lengths of the metacarpals and metatarsals; areas of calcification in the soft tissues; sometimes some degree of mental retardation. These patients responded to dihydrotachysterol (AT-10) more slowly than do patients with true

hypoparathyreoidism. This substance increases calcium absorption from the bowel and increases phosphorus excretion by the kidney, as does vitamin *D*. In this disease administration of vitamin *D* in large doses and calcium by mouth is the treatment of choice, and it seems to be as effective as and certainly cheaper than the use of AT-10.

ORTHOPÆDIC SURGERY.

The Treatment of Trochanteric Fractures of the Femur.

E. M. EVANS (*The Journal of Bone and Joint Surgery*, May, 1949) presents three series of patients with trochanteric fractures of the femur: 101 treated conservatively in hospital (mortality 15%), 25 sent home because of lack of hospital beds (mortality 44%), 22 treated by fixation with a Capener-Neufeld nail-plate (mortality nil). He points out that in the neck of the femur the bone is strongest along the *calcar femorale* where the greatest strain is thrown by the forces of gravity and muscle action, which tend to diminish the angle of the neck of the shaft. After a fracture in this neighbourhood, cortical bone around the *calcar femorale* may remain in apposition; with adequate immobilization the fracture will not then collapse. But when the cortical bone is overlapping, or when it is comminuted in such a way as to form a gap on the inner side, there is no resistance to collapse and *coxa vara* deformity is to be expected. This is borne out in practice. In the series now under review, *coxa vara* developed only in cases with cortical overlap or cortical destruction in the region of the *calcar femorale*; when cortical overlap was corrected during reduction the fracture became stable. The author classifies trochanteric fractures into two main types depending upon the general direction of the fracture. In Type I fractures the fracture line runs upwards and outwards from the region of the lesser trochanter. There are four subdivisions of this type: in the first (65% of all cases) the inner cortical buttress has never been disturbed, there is no displacement, and the fracture unites in perfect position; in the second, simple overlap of the inner cortical buttress can be reduced by manipulation, and the fracture thus becomes stable; in the third and fourth there is unreduced overlap or destruction of this cortical buttress and *coxa vara* deformity is to be expected. In Type II fractures (8% of cases in this series) the line of fracture is the reverse of that usually found, corresponding roughly with the line of a McMurray osteotomy. The author states that the incidence of *coxa vara* deformity is not diminished by operation; it occurs in about 21% of cases. The strong forces inherent in the muscles around the hip joint are even greater than the strength of the nail, and internal fixation without external protection will not always prevent deformity. It is doubtful whether any attempt should be made to prevent the bones collapsing if the nature of the fracture is such as to demand it. Patients treated conservatively stayed in hospital fifteen weeks, those treated by operation four weeks. The author believes that a case can be made for operative fixation of these fractures as a routine treatment. Exception, if any, will not be in the later age groups, but among younger patients. Patients under the age of sixty years tolerate prolonged immobilization well; but even in the young the comfort and mobility of the patient, and the economic factor of length of stay in hospital, should usually outweigh reluctance to operate on a closed fracture. The technique of the nailing procedure and the prognosis as regards stability after nailing are discussed.

Arthrodesis of the Hip Joint.

F. E. STINCHFIELD AND W. U. CAVALLARO (*The Journal of Bone and Joint Surgery*, January, 1950) have analysed the results in 117 cases of hip arthrodesis and found that the pseudarthrosis rate for the entire group was 23% and the mortality rate 3·4%. All deaths occurred in the osteoarthritis group. The rate of infection was 6%. The authors state that not all pseudarthroses are incapacitating. Of the 15 patients in this series in whom pseudarthroses ultimately developed, eight patients were relatively free from symptoms. Back pain was present in all age groups following arthrodesis. The gait was deliberate and acceptable in patients with neutral abduction-adduction without shortening. The most normal gait resulted in patients with very slight adduction and no shortening. The poorest gait was in patients with equal limb lengths and abduction; this created a relative lengthening of the fused side, not compensated for by the opposite extremity. The authors suggest that the most certain method of producing arthrodesis is either by intraarticular fusion *plus* a bone graft *plus* a nail of the Smith-Petersen type for internal fixation, or by intraarticular fusion *plus* the insertion of three vitallium nails. They state that the first attempt to repair pseudarthroses of the hip resulted in 50% of failures.

The Sensitivity and Innervation of the Articular Capsule.

J. H. KELLGREN AND E. P. SAMUEL (*The Journal of Bone and Joint Surgery*, February, 1950) have studied pressure as well as pain sensibility in the knee joints of normal human volunteers and of patients undergoing arthrotomy under local anæsthesia and have combined these studies with detailed examination of the innervation of human and feline knee joints. They found that the fibrous ligament was a highly sensitive structure, containing many spots which gave rise to sensations of pain or pressure when stimulated mechanically or chemically. Synovial membrane was found to be a relatively insensitive structure which only occasionally contained pain-sensitive spots. Histological examination of articular capsule from the knee joints of normal and sympathectomized cats showed that articular ligaments have a rich nerve plexus and a variety of specialized and unspecialized nerve endings, most of which are somatic in origin. Synovial membrane contains a more delicate nerve network and also a variety of nerve endings, the majority of which are autonomic in origin. But a substantial number of somatic nerves enter the synovial membrane, some of which terminate in nerve loops, globular endings or simple unspecialized endings. Histological examination of normal human articular capsule showed that its innervation closely resembled that of the cat, but no human material was examined after sympathectomy. The authors state that the fibrous ligaments play an important role in articular sensation and appear to be the major source of joint pain. Synovial membrane is not a major source of articular sensation and probably contributes little to the symptoms of joint disease.

Footballer's Ankle.

T. P. MCMURRAY (*The Journal of Bone and Joint Surgery*, February, 1950) describes footballer's ankle as an injury peculiar to the professional "soccer" footballer, especially those over the age of twenty-five years who have played the game for several years. Unlike many ankle injuries incurred by footballers, it is the result of repeated minor strains of the anterior ligament of the ankle joint. It is characterized by pain and tenderness localized to the area of strain. Radiographic examination shows a bony outgrowth into the capsule of the joint from the anterior margin of the tibia or from the upper surface of the neck of the astragalus. Liability to ligamentous strain arises from the position of plantar flexion in which the foot is held at the moment of contact with the ball, especially when the ball is "dead". In order to control the direction of a football the foot must be held in the full equinus position to ensure the largest possible area of contact between the foot and the ball; the extensor muscles which normally protect the dorsal capsule of the ankle joint are at a mechanical disadvantage, and the strain of the blow is borne largely by the ligament itself. In Association football this position is used constantly in kicking the ball; in Rugby football it is used only in drop-kicking. In punting and place-kicking the joint is in a less degree of the equinus position, and it is protected by the extensor muscles. The patient is able to kick the ball as well as ever when using the point of the toe, but when attempting to kick it in the correct manner he feels a sudden stab of pain in front of the joint. Slight swelling may appear over the anterior aspect of the ankle, but as a rule the joint looks normal. There is a point of tenderness in front of the lower margin of the tibia; forced passive plantar-flexion causes pain. Radiographically in the early stages there may be nothing more than slight periosteal roughening on the anterior aspect of the lower end of the tibia. Later, a bony ridge may be seen extending forward from the surface of the tibia at the level of attachment of the anterior capsule of the joint. A similar bony outgrowth may project upwards and slightly backwards from the neck of the astragalus. Owing to the position and extent of the bony rim the radiographic appearances are suggestive of osteoarthritis of the ankle joint with lipping of the articular margin of the tibia, but in fact the articular surfaces are not involved and the outgrowth lies slightly above the articular margin, which is always clear and unaffected. The treatment is removal of the mass of bone usually in the anterior ligament. None of the patients operated upon have had to retire from football and all have resumed their former positions. In no case has this condition been cured by physiotherapy.

British Medical Association News.

SCIENTIFIC.

A MEETING of the New South Wales Branch of the British Medical Association was held at the Royal Prince Alfred Hospital on May 18, 1950. The meeting took the form of a series of clinical demonstrations by members of the honorary medical and surgical staffs of the hospital. Part of this report was published in the issue of September 9, 1950.

Abdominal Tumours.

DR. N. R. WYNDHAM showed three male patients with lower abdominal tumours. The first was a man, aged seventy-six years, with twelve months' history of diarrhœa and the passage of blood *per rectum*. X-ray examination after barium enema disclosed a typical filling defect on the lateral wall of the caecum. In addition he had severe secondary anæmia, his hæmoglobin value on admission being under five grammes *per centum*. After correction of his anæmia, it was proposed to resect his carcinoma, as clinical examination disclosed a small painless mobile mass in the right iliac fossa.

The next patient, who was aged fifty-two years, had only one month previously noticed progressive painless enlargement of his abdomen. Physical examination disclosed a large retroperitoneal tumour, from which a biopsy was taken. It proved to be a neuro-fibrosarcoma. At the time of the meeting the tumour had grown to fill almost the entire abdomen, but in spite of this there were surprisingly few subjective symptoms.

The last patient, who was aged seventy-three years, had an abdominal tumour situated in the suprapubic region and arising in the pelvis. This was not altered by catheterization of the bladder. Rectal examination disclosed a mass extending upwards from above the upper border of the prostate, which did not itself appear to be enlarged. Microscopic examination of the urine revealed no abnormality. The serum acid and alkaline phosphatase levels were within normal limits. X-ray pictures of the pelvis and lumbosacral spine were normal. The result of excretion pyelography was normal. There was a leucocytosis of 20,000 cells per cubic millimetre on the patient's admission to hospital, and he had had an irregular, low-grade pyrexia since his admission. Dr. Wyndham considered that the mass was probably due to an appendix abscess.

Stricture of the Common Bile Duct.

DR. S. H. LOVELL discussed the case of a female patient, aged forty-five years at the time of the meeting, who had undergone operations for the repair of a stricture of the common bile duct following cholecystectomy. This woman had had her gall-bladder removed some five and a half years previously. After the operation she had been in indifferent health for the first few months, her symptoms in some way suggesting unresolved pneumonia at the base of the right lung.

Approximately five months after operation, jaundice was noted. This deepened progressively, and hepatomegaly developed. When first examined some nine months after cholecystectomy, she was cachectic and deeply jaundiced, and the lower border of the intensely hard liver was at the level of the umbilicus. A diagnosis of stricture was made, and after the usual preparation, laparotomy was performed. The stricture was at the usual site, the area of the junction of the cystic common bile ducts, and was gross. The degree and firmness of the hepatomegaly precluded any form of "permanent" repair, so a rubber tube was passed into the dilated bulbous stump of the common hepatic duct and the contracted distal segment of the common duct and "overlain" with an improvised cover of tissue from the right edge of the gastro-hepatic omentum. In spite of her low condition, an excellent recovery followed—so excellent in fact that her jaundice disappeared, her weight increased appreciably, and the liver receded until its lower edge was only just palpable. In this condition, it was somewhat difficult to persuade her to submit to further operations and she absented herself for some twelve months; then she reappeared with jaundice, loss of weight, enlarging liver and a history suggesting recurring episodes of cholangitis. A further operation was agreed to, and this time it was possible to do a little more, but only with very considerable difficulty. The only operation which appeared feasible, in view of the hepatomegaly and fixation of the gastro-hepatic omentum and duodenum, was that described by Monprofit in 1905, and modified more recently by Cattell. Although this operation was performed in 1946, and then with the expectation that her life would not be saved for much more than a year, she had managed to carry on. Her liver was still enlarged to one finger's breadth below the costal margin, and she still had occasional bouts of cholangitis, which had not been relieved materially by the antibiotics, but did clear up on treatment with sulphadiazine. In addition she had developed a peculiar type of primary anæmia, which her physician controlled with injections of liver extract. It was considered that she had a slowly progressing cirrhosis following her stricture and biliary tract infection, and that her prognosis was poor.

Referring to this condition, Dr. Lovell said that it was not at all uncommon, and that one of the major difficulties of the surgeon was to get the patient at an early stage—the earlier the condition was recognized, the greater the chance of successful repair. Ideally, such ducts should be repaired within a month—earlier if possible—but the circumstances rarely made that likely. In early cases, the ideal of end-to-end mucous membrane to mucous membrane anastomosis could be attained. As the time interval increased, the possibility of attaining the ideal diminished, and alternative channels had to be devised. In late cases, such as the one under discussion, Dr. Lovell favoured the Monprofit operation. Although he was hesitant to anchor the jejunal loop to the abdominal wall as occurred when the operation was performed in the way suggested by Cattell, it certainly provided a means of ensuring that the tube remained *in situ* in the reconstructed channel for as long as the surgeon desired. Dr. Lovell pointed out that however well such operations were performed in late cases, there remained the gloomy fact that, once established, infection in the upper part of the biliary tract was most difficult to defeat and, in the end, commonly resulted in progressive cirrhosis which proved fatal. The obvious corollary was that the possibility of this development must be very widely known and appreciated so that an earlier recognition of the condition was made by those performing gall-bladder surgery.

Adamantinoma.

DR. A. E. M. REDDEL presented a married woman, aged sixty-seven years, who complained of a swelling on the right side of her face which had been present for one year. It was gradually increasing in size, but was not painful, and apart from some difficulty with her dentures she had no other symptoms. Her teeth had all been extracted thirty years previously. On examination of the patient, a large, irregular swelling about three or four inches in diameter was found to be present on the right side of the jaw. This involved the ramus and body of the mandible and extended internally into the mouth as well as externally. An X-ray examination revealed a multilocular expansion of the mandible, and the condition was considered to be an adamantinoma.

Acute Frontal Sinusitis.

DR. VOLNEY BULTEAU presented a patient who when first examined had complained of severe pain in the right frontal region for one week. There was a past history of many similar attacks during the previous eight years or more. Bilateral radical antrostomy had been performed seven years before. The clinical findings were pronounced frontal tenderness and a high septal deflection to the right. X-ray examination revealed dulness of the right frontal and both maxillary sinuses. The patient was admitted to hospital the same day and penicillin administration was started. At operation the area of septal deflection was resected, with resultant exposure of polypi completely blocking the fronto-nasal duct. These were removed. Penicillin therapy was continued, but there was still no improvement clinically or radiologically. A right external frontal operation was performed four days later and thick pus, under pressure, evacuated. A drainage tube was left *in situ* for four days and then removed. Freedom from symptoms followed until the present time, when the same frontal headache was starting to appear again. In view of the long past history further operative procedures would probably be necessary.

Hairy Tongue.

In presenting a patient with hairy tongue, Dr. Bulteau explained that the "hairs" resulted from hypertrophy and keratinization of the filiform papilla. It was thought that the disturbance was produced by irritating substances. The presence of bacteria and mycelia was considered to be accidental and not of ætiological significance. The more recent view was that there was a secondary deposit of pigment on and between the papilli from the external sources (foods, medicines, mouth washes, tannic acid and various chemical reactions). Frequently that resulted in a black discoloration. However, another authority felt that the discoloration might be due to an intensification of the normal

colour of the horny structure as the result of age, drying out *et cetera*. In support of this some animals normally presented on their tongue the appearance described, notably the Chinese chow-dog. About 1941 vitamin deficiencies had been incriminated, but subsequently high dosage treatment with vitamins in most cases had failed to control the condition. Antibiotics had been tried with little success. The condition seemed resistant to most forms of treatment. The histological appearance showing the zone of mycelia and bacteria which surrounded the inner mass of keratin might be seen in the photographs.

Otogenic Meningitis.

Dr. Bulteau's last patient was a man who, when examined on February 19, 1947, had complained of right otalgia for three days, pain in the neck and stiffness for two days, right otorrhœa for two days, severe headaches and vomiting for twenty-four hours, and chronic suppurative *otitis media* for many years. Clinical examination revealed a temperature of 103·6° F., a Kernig's sign present on each side, pronounced neck rigidity, mastoid tenderness and a copious purulent discharge from the right ear. The cerebro-spinal fluid was turbid and under greatly increased pressure; 10 millilitres were removed and replaced by penicillin. On the following day right radical mastoidectomy was carried out; cholesteatoma and granulations in the attic were found. On the same day and for the next two days lumbar puncture and intrathecal introduction of penicillin were continued daily. On February 23 the temperature was normal and there were no abnormal neurological signs. The subsequent course was uneventful. The post-auricular wound was resutured. The patient had since been employed as a horse breaker in the far north-west of New South Wales and was free from symptoms.

Cranial and Intracranial Suppuration following Frontal Sinusitis.

DR. R. A. MONEY presented a male patient, aged twenty-one years, who had been admitted to the neurosurgical department of the Royal Prince Alfred Hospital on April 12, 1949, from the Prince Henry Hospital, with a history of a mild head injury some two months previously. One month before the time of admission proof puncture of the left antrum had revealed the presence of thick pus. A week after this he had to be admitted to Prince Henry Hospital with meningitis from which he recovered rapidly, but two days before his admission to Royal Prince Alfred Hospital he was readmitted to Prince Henry Hospital with severe headaches and right hemiplegia. Shortly afterwards he became unconscious, and Jacksonian fits commenced involving the right side of his face and arm and recurred with increasing frequency up to every five minutes. On examination, the patient was comatose and Jacksonian fits were recurring at frequent intervals involving the right side of his face and the right upper limb. A burr hole was placed in the left fronto-temporal region, and on opening of the dura, thin yellowish pus gushed out of the subdural space. As much as possible was evacuated by suction and lavage, and a catheter was left in the space through which penicillin could be introduced at frequent intervals. With the aid of sulphadiazine and antibiotic therapy, together with lavage and drainage, recovery from the subdural abscess occurred, and by April 21 his condition was satisfactory. X-ray examination of his sinuses revealed no evidence of osteomyelitis, but the left antrum was dull, and when it was washed out by Dr. A. O. Davy, only a few shreds of mucopus were obtained. On May 3 pneumoencephalography was performed, but no evidence of any brain abscess was obtained. A few days later the patient began to complain of severe frontal headaches and was tender over the right frontal region. Skiagrams of his skull now showed a definite area of osteomyelitis extending upwards from the right frontal sinus [the skiagrams were shown], and bilateral radical frontal sinus operation with complete removal of the area of osteomyelitis in the frontal bone was performed by Dr. A. O. Davy on May 7. At the same time a large extradural abscess was found in the right frontal region, extending over the anterior portion of the longitudinal sinus. Following this extensive procedure, the patient's convalescence was uneventful, and he left hospital with the wound completely healed on June 17. He was readmitted to hospital ten days later in a semiconscious condition suffering from a severe headache and vomiting at frequent intervals. He had also taken several epileptic fits, which involved the right side of his body. Early papilœdema was noted, but no other abnormalities. Electroencephalography gave a highly abnormal record, which suggested an abscess in the left frontal lobe. There was a bulge at the site of the original burr hole in the left fronto-temporal region, and when this was reopened at operation no abscess was found in the subdural space, but on needling of the brain a large abscess was located in the left frontal region. It was evacuated, and 10,000 units of penicillin and one millilitre of thorotrast were introduced. X-ray films (pyograms) were then taken and showed the outlines of the abscess cavity. The abscess was aspirated and penicillin instilled on several subsequent occasions, and skiagrams were taken at intervals which showed the capsule of the abscess to be becoming denser and more crenated and the cavity becoming smaller until it was finally obliterated by about July 22 [serial pyograms were shown]. The patient continued to have "blackouts", but no further fits occurred, and he was discharged from hospital on July 27. Thereafter his condition remained moderately satisfactory, but about December major Jacksonian fits recurred at more frequent intervals. His mental condition became rather dull. Electroencephalography gave an abnormal record with paroxysmal activity in the left frontal lobe. Pneumoencephalography showed that the anterior horn of the left lateral ventricle was larger than the right and was pulled out as a traction diverticulum towards the rolled-up abscess capsule in the left frontal lobe. This being considered the focus for his epileptic fits, the crenated abscess capsule with the surrounding area of the left frontal lobe was resected at operation on January 26, 1950. With the help of sulphadiazine and the antibiotics, healing after this procedure was uneventful, and the patient was able to leave hospital on February 17. Electroencephalography performed on the previous day still gave an abnormal record indicating an epileptogenous activity in the left frontal region. Activity was much less than in the previous record. Since leaving hospital he had had an occasional fit, but otherwise his condition had been satisfactory. Thus, this patient had survived meningitis, subdural abscess, osteomyelitis of the frontal bone, extradural abscess and intracerebral abscess. The infection was apparently due to a hæmolytic streptococcus.

Subdural Hæmatoma.

Dr. Money's second patient, a single woman, aged forty-nine years, had been admitted to the Manly District Hospital on December 22, 1949. At that time she was only semiconscious and no accurate history could be obtained, but it was said that she had sustained a head injury when she had been assaulted some four weeks previously, and that she had had intermittent severe headache since, which culminated in a "collapse" the previous day. Lumbar puncture was performed and yielded xanthochromic fluid at a pressure of 250 millimetres of fluid. It was thought that she had papilœdema of both eyes, more on the right than on the left, and the skull was trephined in the right temporal fossa. A small amount of blood was sucked out of the subdural space and the wound was closed. After this procedure the patient's condition improved slightly, but when seen in consultation the next day she was still only semiconscious and would not respond to vocal stimuli. There was slight weakness in the left side of her face and in the left-sided limbs, but otherwise no definite abnormalities were found in her nervous system. She was transferred to the neurosurgical department of the Royal Prince Alfred Hospital, where electroencephalography gave an abnormal record which suggested an incompletely evacuated hæmatoma over the right cerebral hemisphere, especially over the temporal lobe. Arteriography of the right internal carotid artery showed much displacement of both the anterior and the middle cerebral systems to the left, with absence of filling in the small arteries over the surface of the right cerebral hemisphere above the Sylvian fissure. [Skiagrams were shown.] At operation, the old incision in the right temporal region was reopened and extended. The trephine hole also was enlarged, and a large subdural hæmatoma containing both liquid blood and many clots was vacuated as completely as possible. The bleeding appeared to be coming from a vein running from the temporal lobe to the lateral sinus. After the operation the patient regained consciousness and was able to speak normally, but the following day she was again unconscious. The wound was reopened for the second time, and some further fresh blood clot removed from over the temporal lobe. On the third day her condition was still unsatisfactory and she was still unconscious. Arteriography was performed of both the right internal and the left internal carotid systems. On the right side there was still evidence of displacement to the left of both the anterior and the middle cerebral systems, but on the left side they appeared to be in their normal situations. Accordingly, another burr hole was made in the right frontal region, and on opening of the dura a large amount of air and blood-stained fluid escaped under pressure. The under-

lying brain could be seen compressed, so that a drain was left in the wound as it was closed. At the conclusion of this operation, the patient's condition was slightly improved, and thereafter a very slow but gradual recovery took place until she was discharged from hospital on January 23, 1950.

Dr. Money then presented a boy, aged sixteen years, who had received a blow on the jaw while boxing about four months prior to his admission to hospital. He felt dazed and had a headache for a few days. Thereafter, the headache persisted as a dull ache which was increased in severity if he jarred his head. About three weeks before his admission he had awoken with a very severe headache which persisted. He felt nauseated and had no appetite, and during the two weeks before admission had vomited frequently. He was also becoming very drowsy. On examination of the patient bilateral papilloedema was noted in the ocular fundi, but no other definite abnormality. Plain skiagrams of his skull showed no evidence of fracture or other abnormality. Lumbar puncture yielded clear fluid at a pressure of 350 millimetres of fluid, with no abnormal constituents. Electroencephalography showed an abnormal record which indicated the presence of a subdural hæmatoma or cerebral contusion over the right cerebral hemisphere. Arteriography of the right internal carotid system showed a gross shift of both anterior and middle cerebral arterial systems to the left, indicating the presence of a large space-occupying lesion over the right cerebral hemisphere. [Arteriograms were shown.] On March 13, 1950, a burr hole was placed over the right cerebral hemisphere, when a large dark fluid collection of old blood was evacuated from the right subdural space by suction and lavage. A drain was left in the cavity which remained, and during the next few days further amounts of old liquid blood drained out. For the next two weeks his convalescence was satisfactory, although his headaches did not completely disappear and the intracranial pressure remained high. By March 29 the patient's temperature was rising each night, and a repetition of arteriography of the right internal carotid system still showed some displacement of the arteries over to the left. [Arteriograms shown.] Accordingly, on March 30 another burr hole was made in the right temporal region when some old disorganized blood clot and a good deal of pus were aspirated from this portion of the subdural space. The pus contained many pus cells and Gram-negative débris, but no organisms, and its culture produced no organisms. A tube was left in this space for a few days and gradually shortened until it was removed on April 4. Thereafter the patient's convalescence was satisfactory, and he was able to leave for home on April 12.

Meningioma of the Spinal Canal Causing Paraplegia.

Dr. Money's next patient, a married woman, aged seventy-four years, had been quite well until three years previously, when after a fall onto her back she noticed pains about the level of her waist, which subsequently radiated down her legs. After this her legs gradually weakened, and she was compelled to use a walking stick. But, about six months before the meeting, after another fall onto her knees, she found that she could not walk even with the help of a walking stick. About this time she lost sensation in her lower limbs, and the control of her bladder and bowels became difficult. She had been bedridden for some time and was unable to feel the sheets touching her legs. She could move her lower limbs a little, but at other times spontaneous movement occurred with a severe pain in the region of the knees. Recently she had become incontinent of urine. She was admitted to the Royal North Shore Hospital on March 6, 1950, under Dr. Hales Wilson. Examination there revealed the presence of almost complete paraplegia from the level of the umbilicus downwards with a good deal of wasting in the muscles of her lower limbs. Sensations of touch, pain, temperature and passive position were all impaired below the level of the eighth thoracic segment. The plantar reflexes were extensor, and the tendon reflexes were all somewhat diminished. At lumbar puncture the results of Queckenstedt tests were found to be negative, and the protein content of the cerebro-spinal fluid was 200 milligrammes *per centum*. On March 15 she was seen in consultation, and a provisional diagnosis of spinal cord tumour was made. She was subsequently transferred to the neurosurgical department at the Royal Prince Alfred Hospital, where myelograms, after the introduction of "Pantopaque" into the spinal canal, demonstrated a complete hold-up at the level of the seventh thoracic vertebra. [Myelograms were shown.] The operation of laminectomy was performed on April 13, 1950, when a large meningioma was found to be firmly attached to the dura at the level of the seventh thoracic vertebra. This attachment was ossified. The tumour was compressing the spinal cord at this level, but was removed intact together with the attached portion of ossified *dura mater*. The cord itself looked very thinned out after the tumour had been removed, so that the prognosis was not considered to be a good one. The patient's condition did not permit of the gap in the dura being grafted with *fascia lata*, and the wound was closed firmly. Healing occurred by primary intention, and convalescence was uneventful. Since operation the patient had recovered a good deal of voluntary power in her lower limbs and could walk with assistance. At lumbar puncture performed on April 29 the results of Queckenstedt tests were positive. The cerebro-spinal fluid contained only 50 milligrammes of protein *per centum*. Dr. Money said that the final outlook for the patient was not good, owing to the length of time the tumour had been present and the size to which it had grown, but further improvement should still occur.

Ruptured Aneurysm of the Right Internal Carotid Artery.

Dr. Money's last patient, a man, aged nineteen years, had been involved in a brawl on February 19, 1950. It was alleged that he had been punched on the right side of the jaw and then kicked on the head. He was admitted to the Canterbury District Hospital in an unconscious and intoxicated condition. He vomited a good deal and recovered consciousness about eight hours later. The following day his left arm was flung about in an aimless fashion, and the patient himself was very noisy, restless and quite irrational. This state of affairs persisted until February 25, when he developed complete paralysis of the left upper and lower limbs, following a severe headache. His neck was very stiff, and the plantar reflex on the left side was extensor. At lumbar puncture, blood-stained fluid was obtained under increased pressure. After this, his condition improved somewhat, but he remained hemiplegic on the left side and his mental condition was very difficult. He was noisy and irrational, as well as quite incontinent of urine and fæces, and he persisted in distributing his fæces around the bed. Whenever any splints of plaster of Paris or other type were applied to his left hand and foot, he proceeded to demolish them or pick them to pieces with his right hand. He rambled considerably and at times talked gibberish. He was transferred to the neurosurgical department of the Royal Prince Alfred Hospital on March 10. Examination revealed the presence of left hemiplegia with the hand held in the position of *"main en accoucheur"*. Both limbs were held extremely rigidly, and at times the impression was gained that the paralysis was functional; but the left abdominal reflex was absent and the plantar reflex on the left side was definitely extensor. Sensation also appeared to be absent, but as the patient was extremely uncooperative the accuracy of sensory testing was doubtful. Lumbar puncture yielded clear fluid at a pressure of 210 millimetres of fluid, but it contained no abnormal constituents. Electroencephalography gave an abnormal record which was consistent with a subdural hæmatoma or a severe cerebral contusion in the right frontal region. Pneumoencephalography showed a pronounced dilatation of the whole of the ventricular system to grade II hydrocephalus without any deformity or displacement, possibly the result of deficient absorption, as all the subarachnoid pathways appeared to be blocked. [Pneumoencephalograms were shown.] Arteriography of the right internal carotid system was then performed, and an aneurysm was seen in the internal carotid artery just before its bifurcation into anterior and middle cerebral arteries. [Arteriograms were shown.] It was felt that this aneurysm must have leaked either directly into the subarachnoid space or into the right cerebral hemisphere itself shortly after the original injury and been the cause of the hemiplegia. On March 31 arteriography was performed of the left internal carotid system, while the right internal carotid artery was compressed. Filling of both right and left internal carotid systems was obtained, indicating that it would be safe to ligate the right internal carotid artery. [Arteriograms were shown.] On April 3 the right internal carotid artery was clamped and electroencephalography performed for thirty minutes without any significant change occurring in the record from the right cerebral hemisphere. A right fronto-temporal bone flap was then turned down and the aneurysm exposed after retraction of the right frontal lobe. The aneurysm was being defined, in an endeavour to place a clip around its neck, when it burst, and profuse hæmorrhage occurred. This was controlled somewhat by immediate ligature of the right internal carotid artery, but not completely until the cavity of the aneurysm was plugged with a large piece of muscle obtained from the right calf. During this procedure it was found necessary to give several litres of blood. The patient's convalescence was uneventful, and the wound healed by primary

intention. Since operation, recovery had been gradual, and he was able to leave hospital on May 10, quite rational mentally, but still with some evidence of left-sided hemiplegia; this was still decreasing, so that he was able to walk with a stick.

Bilateral Frontal Leucotomy.

DR. G. E. PHILLIPS, before showing a series of patients to illustrate the results of bilateral frontal leucotomy, said that without full control and personal survey of the pre-operative and post-operative environment over a long period, it was most difficult to assess the effect of bilateral trans-frontal leucotomy in the treatment of psychiatric disease. In practice one had to rely largely upon the observations of relatives and friends, which were not uncommonly over-enthusiastic. However, in some cases the result had so obviously benefited the patient that the merit of the operation became clear from a consideration of the history alone. That was particularly so with patients who had been certified either repeatedly or for a long period, or who had shown transient improvement after electroconvulsive or insulin therapy, or who had regressed rapidly and had not been able to take a relatively full part within their customary environment. The patients to be shown demonstrated the results in that type of case. It was necessary to state that considerable medico-legal difficulty had arisen in performing the operation on patients who were actually under certification. It would appear that under existing legislation very considerable legal responsibilities were undertaken by the surgeon performing the operation, their nature being such that the responsible medical officers at mental hospitals were unable to take any part in referring patients for surgical treatment. It had been Dr. Phillips's practice to depend upon the opinion of a consultant psychiatrist as to the suitability for surgical treatment in each case, and where necessary to advise the parents or next-of-kin of patients under certification to seek legal opinion on the patient's behalf before the operation was performed. The surgical technique was established on the physiological basis of the anatomical communications which had been shown to exist between the thalamus and the cortex of the frontal lobe by Le Gros Clark. The operation was designed to cut the projection fibres from the dorso-medial nucleus of the thalamus to the prefrontal cortex, and thereby to abolish or modify the patient's affective tone, to release emotional tension and to reduce agitation or depression. The operation was a simple one. The period of time spent in hospital was one week, and up to the present time no deaths had occurred as the result of the operation.

The first patient presented by Dr. Phillips was a man, aged thirty-one years, who had been first examined on January 24, 1949, when it was stated that he had been suffering from schizophrenia for five years. He had been discharged from the army in 1944 because of depressive psychosis. He was in the military hospital at Concord and was transferred to Kenmore Mental Hospital. After some months he was discharged from hospital, and was employed for six months as a metal worker. He was then readmitted to the Concord hospital for electroconvulsive therapy, and remained well for some months until June, 1946. At that time he became stubborn and quite unmanageable, and was again admitted to the Concord hospital for further electro-convulsive therapy; this having produced no improvement in his condition, it was followed with a course of insulin shock therapy. He was discharged from hospital, improved, and worked as a painter for some months until May, 1947, when he lost interest in his work, began to drink and stated that people were interfering with him and listening on his wireless beam. He was certified and sent to Callan Park Mental Hospital in August, 1947, and was allowed out in November on leave as he had improved again. After a few months his condition deteriorated, and in May, 1948, he became violent and destructive. He was returned to Callan Park hospital, and had been there until he was admitted to the Royal Prince Alfred Hospital while on leave. At Callan Park hospital he had been very violent, had broken his hand twice, and had received numerous "black eyes" and contusions. His previous history revealed that he had had a successful school record, but had experienced a "nervous breakdown" at the age of eighteen years. His war record was good. His father had been a voluntary patient in Broughton Hall on two occasions. The patient was married, had a daughter aged eleven years, but had divorced his wife, who he had discovered was a woman of loose morals. The patient was interviewed in consultation with Dr. Cedric Swanton, who stated: "No doubt he is a suitable case for leucotomy. However, he says he is perfectly all right and that he does not want any operation, and that nobody is going to interfere with his head. He appears to have little insight, and I doubt if he is volitional. Consequently the propriety of doing the operation from the legal point of view is doubtful." Legal advice was sought on the patient's behalf, and the opinion was given that the operation would be legal. The matter was discussed with the patient, and written permission obtained from him for surgical treatment. On February 22 bilateral transfrontal leucotomy was performed. Post-operative convalescence was uneventful. The follow-up note of February 28 stated: "The patient is well and has acquired a 'sunny nature', and his friends are much pleased with the result of the operation." He was discharged from hospital on March 2. Since the operation the patient's conduct has apparently been quite normal. He boarded with a friend at Paddington, who regarded him as "completely cured". He had put on over two stone in weight, and had been working continuously as an assembler in a radio factory from a few weeks after the operation, up to the time of the meeting.

The next patient was a young woman, aged twenty-five years, the daughter of a naval officer. It was stated that she was quiet and refined in disposition as a child, gained a bursary at the age of eleven years, was five years at the Saint George High School, obtained her Intermediate and Leaving Certificates with honours, and was employed subsequently as a stenographer on the staff of an insurance company. In 1940 it was noticed that she had become untidy, had lost interest in her work, and was unable to concentrate. She became interested in astrology, and her behaviour was largely guided by reference to astrological charts. She was examined in late 1940 by Dr. J. A. McGeorge, who diagnosed her condition as schizophrenia, and she was admitted to Broughton Hall, where she had a series of electroconvulsive shocks. Her condition improved, and she was discharged from hospital after three months. She returned to work for about twelve months; her symptoms recurred and she was readmitted to Broughton Hall, where further electroconvulsive therapy was given. No improvement occurred, and after six months she was certified and admitted to Callan Park Mental Hospital. Her behaviour was very bad—she was wild and impulsive and would throw articles about and punch out with her fists. On her twenty-first birthday she tossed the entire afternoon tea over her parents. Further electroconvulsive therapy was given, but she did not respond. She was transferred to Morrisset Mental Hospital in 1943, and given further electroconvulsive therapy without effect. She was still quite unmanageable, was dirty in her habits, and spent a lot of her time wandering around restlessly, taking off her clothes. She was transferred to a private hospital, and was given a course of insulin shock therapy. This was ineffectual, and her behaviour was still impulsive and violent. It was necessary to transfer her to the Reception House, and she was subsequently transferred to Morrisset Mental Hospital again. She was examined by Dr. C. H. Swanton, Dr. A. T. Edwards and Dr. C. M. McCarthy, all of whom recommended transfrontal leucotomy. While on leave she was admitted to the Royal Prince Alfred Hospital, where the patient consented to operation, and written permission for this procedure was obtained from the parents, who had been advised of the legal background. Bilateral transfrontal leucotomy was performed in January, 1947. Convalescence was uneventful, and the patient was discharged from hospital a week after operation. There was an immediate change in her conduct and appearance, and on February 1 the parents reported that she had resumed playing the piano and had become vivacious and again interested in her previous friends and their activities. There was a complete absence of any aggressive or impulsive tendencies. Nearly twelve months after the operation her parents made the following report: "Her behaviour is quite normal, and she is full of the zest of life, displaying an abundant sense of humour, and more confidence than she had before the illness. Every Friday night she plays tennis and mingles with the young people, taking her place as a normal member of society. She has returned to her typing and has recently been preparing specifications for her sister's home-to-be." On May 5, 1950, the parents again reported that her normal conduct had continued; she had become a skilled pianist, in both classical and dance music, she had been attending a business college for three days a week for a refresher course in stenography, and at the examination at the conclusion of this course she had come top with a mark of 95%. Dr. Phillips commented that the patient was now apparently a good-looking young woman who obviously took great care of her personal appearance, and was an interesting and amusing conversationalist.

Dr. Phillips then showed a girl, aged eighteen and a half years, whose parents stated that she had been a normal, intelligent child, who had had good school reports and was well-behaved at home. She left school at the age of sixteen

years, having passed the Intermediate Certificate examination. She commenced to attend a business college course, but after some months came home one day crying and stated that she did not like the people there, and would not go back. She became depressed and relinquished her previous activities. She had been fond of dancing and fishing and used to make her own clothes. However, she became uninterested, and would do nothing. She commenced to suffer delusions and thought the woman in the flat above was talking about her and "knew all about her". She was admitted to Broughton Hall, diagnosed as having a schizophrenic condition, and treated by a course of electroconvulsive shocks. She improved temporarily and was discharged from Broughton Hall, but three weeks later she disappeared. She was found by the police and was taken to the Reception House, was certified and was later admitted to Gladesville Mental Hospital. She had become aggressive, had temper tantrums and used to throw things about. She would not answer when spoken to, and had become dirty in her habits. She was stated to be periodically extremely restless and impulsive. After the parents had been advised and satisfied themselves as to the legal position, the patient was admitted to the Rachel Forster Hospital, while on leave, on October 16, 1949; there bilateral transfrontal leucotomy was performed on October 21. She was discharged on November 1, having shown definite improvement immediately after the operation. She was now quite communicative and displayed no restlessness or impulsive behaviour. On November 24 there was a remarkable change in her appearance, and the parents advised that she had commenced to visit her friends again and was actively helping in the work of the house. She had again taken up sketching, in which she had been previously interested. She was able to hold an interesting and intelligent conversation, and was apparently quite a normal person. In March, 1950, it was learned that she had joined a social club, and was playing tennis regularly each week. On her own initiative she went alone to the Technical College, and after making inquiries had arranged to take the course in commercial art.

When interviewed again in May, 1950, she was very well and had further increased her activities. She had joined the church youth movement, was playing tennis regularly, and attended a physical culture class once a week. She went swimming with her friends, and did the shopping for the household. She had taken to learning typing, and was having singing lessons regularly

Dr. Phillips's last patient was a lad, aged nineteen years, who had been referred by Dr. Cedric Swanton. Dr. Phillips said that the history might perhaps best be given by reference to a recent letter by Dr. Swanton, which stated:

> This boy was first seen at the age of 17, his symptoms having been in existence for some twelve months. He was suffering from extremely acute anxiety hysteria, was unable to leave his home, other than just sprinting distance from his front door. He was quite unable to travel away from home alone and could not go in trains, trams, buses, etc. He could work, which he did in a garage, because it was more or less next door. The guilt basis of his symptoms was precipitated twelve months previously when going up to the back-yard lavatory he found his father hanging by the neck from the rafters of the lavatory roof. This boy's acute symptoms of anxiety were as extreme as any I have seen and were accompanied by gross hyper-excitability of his autonomic nervous system with concomitant somatic visceral reference, particularly to his stomach and bowels. This was expressed as anorexia and vomiting and diarrhœa. Sedation was ineffective unless given to the point of alteration of consciousness. He was treated in Broughton Hall, but his anxiety prevented him from continuing his treatment and he was discharged. He subsequently, I understand, was given deep insulin therapy, which improved his physical condition, but he remained in the same highly agitated state. On three occasions I attempted to treat him in Prince Alfred, the intention being a so-called "electric leucotomy", but his anxiety prevented him from remaining in hospital any more than twenty-four hours. I attempted to treat him in a similar fashion as an outpatient, but again his anxiety was such that he could not attend. At all times he was extremely co-operative, but he was unable to leave his home for treatment. Psychotherapy in the nature of analysis was quite impossible for him, as his anxiety would not allow him to attend for treatment. Finally, his anxiety, with its visceral accompaniments, rendered him so incapacitated and in such a pathetic state, that I felt justified, despite his tender years, in suggesting that the only possible way of relieving his tension was by lobotomy. The patient readily agreed and he was prepared to do anything to get relief of his symptoms. I asked Dr. Gilbert Phillips to do this, which he did with dramatic success, but not without considerable difficulty in his management for the twelve hours in hospital prior to his operation, as Dr. Phillips will no doubt tell you. I saw this boy subsequently when he had complete relief from his anxiety and was able to go out and about unaccompanied, travel in trains and buses, etc., was able to resume employment and made application to do his test to become an N.R.M.A. scout. He apparently suffered no intellectual deterioration, appeared to have a normal response, and the fact of his making application for a job seemed to indicate that he possessed the ability to think and plan ahead. An enquiry from his mother produced the bald and satisfied statement that he was cured.

Dr. Phillips said that the patient had reported to the clinical meeting that night, having made his own way there, and being prepared to wait and face a considerable audience, while the history of his previous condition of agitation was being described.

(To be continued.)

Special Correspondence.

LONDON LETTER.

FROM OUR SPECIAL CORRESPONDENT.

"The Tuberculosis Tragedy."

UNDER this caption a leader in *The Practitioner* for August opens as follows:

> It is an appalling commentary upon the efficiency of the much vaunted National Health Service that, according to a provincial morning newspaper, the Minister of Health has informed a local correspondent that "the present Tb. rate was the biggest plague for 200 years, but regretted that he had no money or nurses to spare". The situation is indeed desperate, with the waiting list for tuberculosis sanatoria now over 11,000. What is incomprehensible to practitioners is that the responsible Minister can make such a statement as this when in one year he spent practically £50m. on dental services, and £25m. on the supplementary ophthalmic services, not to mention over £300,000 on hearing aids, £125,000 on wigs, and £500,000 on advertising in the press for vacancies on hospital staffs for non-teaching hospitals in England and Wales.

It is felt that this quotation from a responsible medical journal summarizes the position so admirably that no excuse is needed for its length. The lay Press is backing wholeheartedly the medical journals in this crusade. Thus *The Spectator* points out that there are some 1000 vacant beds in first-class Swiss sanatoria. At Montana Hall, of which the medical director is an Australian, Dr. Hilary Roche, only one-third of the beds are occupied, and the hospital is in danger of closing for lack of patients, despite the fact that the charges today, in Swiss francs, are practically the same as in 1939. *The Spectator* feels that all these empty beds could be filled at once if the grants previously made to local authorities were renewed by the Minister of Health; £500,000 a year would cover the total cost, and the Swiss authorities would welcome the arrangement. A brief reference was made to this plan in a previous letter (THE MEDICAL JOURNAL OF AUSTRALIA, March 25, 1950, page 416). Dr. Roche feels that "scarcity of hard currency is obviously not an obstacle which could prevent hundreds of British patients from having early treatment in this country, as one and a half million pounds more than last year were allotted this year to British tourists in Switzerland" (*British Medical Journal*, July 29, 1950, page 295). The death rate from tuberculosis is much greater than that from road accidents, and *The Times* quotes the Minister as stating that the waiting period for admission in some areas was twelve months. The chairman of the medical committee of the National Association for the Prevention of Tuberculosis recently said that approximately four people in every 1000 of the population examined by mass radiography were found to suffer from active tuberculosis. The Minister of Health has urged hospitals and local authorities to reduce in every way possible the waiting periods for beds and mentioned the combination of home

treatment with short periods as an in-patient, the linking of after-care treatment with clinical work, the utilization of mass radiography as a means of discovering latent cases of infection, suitable occupational resettlement, and the making available of beds in general hospitals and isolation hospitals. This circular has received guarded commendation from two medical Members of Parliament in a letter to *The Times*; they regard it as setting out a long-term policy, but, at the same time, press for the utilization of the empty beds in Swiss sanatoria to meet the present need. Another Member of Parliament asks: "If Holland can maintain, as she does, 200 beds for T.B. patients in Switzerland, why should Great Britain allow a British-run sanatorium in Switzerland to close down for lack of funds, at a time when 11,000 T.B. patients are awaiting admission to sanatoria?" The leader from *The Practitioner*, quoted above, after urging on the Minister the use of the Swiss beds, closes with the acid comment that "after all, his colleague at the Treasury can speak from personal experience of the advantages of medical treatment in Switzerland".

"Kind Nature's Signal of Retreat."

The appearance of an annual report is always a matter of interest, especially when it refers to vital statistics. The Registrar-General has just issued his statistical review for 1948, and some of the figures are given hereunder. Previously 1930 had long held pride of place as the healthiest year, with a death rate of 11·4 per thousand of the civilian population, but 1948 now leads with 11 per thousand. The total number of deaths in 1948 was 468,645, a decrease of roughly 47,000 on the preceding year. As clinicians know, deaths due to coronary artery disease and *angina pectoris* are increasing steadily, the figures being 15,409 (1938), 28,580 (1946), 33,168 (1947) and 36,640 in the year under review. More accurate diagnosis and certification may have some bearing on the later figures, when they are compared with those of ten years ago. Cancer in one form or another is also on the increase, more particularly among males: female mortality decreased over the last two years. The figures for both sexes run as follows: 13·9% of deaths in 1938, 15·1% in 1947 and 79,432 deaths (16·9%) in 1948. The value of preventive inoculation is seen when the figures for deaths from diphtheria are considered: 2861 (1938), 242 (1947) and 155 (1948), a fall of 95% over the ten-year period. This improvement also has a bearing on deaths in the first year of life, 43 per 1000 in 1946, 41 per 1000 in 1947, 34 per 1000 in 1948, and a provisional figure of 32 per 1000 is estimated for 1949. Figures refer to related live births. The recent publication in the lay Press of extracts from medical journals on the connexion between certain preventive inoculations and infantile paralysis has not unnaturally made parents unwilling to have their children protected against the lesser danger in case a greater tragedy may follow. Already reports show a significant drop in the number of children in the early years of life submitted for prophylactic inoculation. "The fate of the immunization campaigns, which have been so brilliantly successful, may well be jeopardized by hasty speculation. To answer these questions with some feeling of conviction will require the conduct of extensive field surveys, which should not be long delayed. In the meantime it would seem best to take advantage of the seasonal incidence of poliomyelitis and restrict mass inoculation to the non-epidemic periods of the year" (*British Medical Journal*, July 1, 1950, page 29). In view of the prominent part played by B. P. McCloskey, of the Victorian State Health Department, in focusing attention on this problem, Australia may claim to have a special interest in the present discussion.

The Isle of Wight is much in the news as regards this disease, but the County Medical Officer of Health has pointed out that a number of the cases have been in visitors who arrived already infected. Some 80,000 persons arrive each week during the holiday season, and even then cases have occurred in only 22 out of more than 28,000 houses. He feels that "the hazards of a holiday on the island are not greater than anywhere else in the country". Taking England and Wales as a whole, cases reported in the week ending August 12 run as follows: 392 (1950), 254 (1949), 39 (1948) and 624 (1947); total deaths so far this year to date are 218, as compared with 624 in 1947, the peak year.

"Now Comes the Tug of War."

The majority of the professional men working the National Health Service are not satisfied, to put it mildly, about their rates of pay, and this may be said to apply most forcibly to those who have had Ministerial cuts. The President of the British Dental Association at the annual meeting is reported as stating that "the recent cuts in remuneration in the general dental service had tended to discourage the best type of men from giving their best. Surely the Ministry could devise a simple means of curtailing excessive earnings without causing thousands of conscientious men to suffer". The Scottish chemists have passed from words to deeds and have taken the matter to the courts. On July 26 the Court of Session granted an interim interdict, which will prohibit the executive councils concerned from putting into effect the latest cut of 8% on chemists' bills, as instructed by the Secretary of State for Scotland. According to a report in *The Times* of August 31, 1950, 1300 private chemists in Scotland were to give three months' notice from September 1, 1950, of their intention to withdraw from the National Health Service; this was the result of a decision of the Scottish Pharmaceutical Council. The secretary of the Council said that there were 1492 chemist shops owned privately in Scotland and mandates had been received on behalf of over 1300 of these authorizing the Council to send in their resignations from the National Health Service; more mandates were expected, and the figure might finally be about 1400. The notice of resignation would be withdrawn, the secretary said, if the Secretary of State withdrew his cut and waited for the decision of an arbitration court. The general practitioners have never been happy on the pay question, and the recent rise of eightpence per gallon in the price of petrol has aggravated the position, particularly for those men who work in the country districts; in one area the extra cost comes to £70 *per annum*. Representations have been made on this question to the Ministry of Health, who passed it back to the Treasury, and the chairman of the General Medical Services Committee has described the position of his committee as being passed from one Ministry to another like a shuttlecock. Some 36% of general practitioners are earning under £1000 a year net. It has been stated in the lay Press that the National Health Service costs over £9 a year for each person, of which the general practitioner's share is about twopence halfpenny a week. The cost of living bonus, as allowed by the Ministry, is 40%, though 70% was asked for by the profession when the scheme was introduced. Since then the cost of living has increased by over 200% in such items as maintaining a house, domestic help and value of a motor-car. As a result 100% is a more realistic figure for the cost of living bonus; the 40% paid by the Ministry is quite inadequate and unrealistic. Withdrawal from the service is being carefully considered, and methods to do this are being worked out. The whole question was fully gone into at the Annual Representative Meeting at Southport (*Supplement to the British Medical Journal*, July 22, 1950, page 37). The medical officers of health, through their association, have long been at loggerheads with the Ministry over salary scales, and men have been drifting into more lucrative forms of employment. After disagreement over proposals made some eighteen months ago, the matter has now been referred by mutual consent to the Industrial Arbitration Court on terms agreed by both sides, and the Court's decision will, it is assumed, be binding on both parties. This should end an unhappy position for, as a leader in a recent *British Medical Journal* wisely states, "the 'wage freeze' still remains the Government's policy, but clearly it cannot be allowed to jeopardise the safety of the country's health". It will be seen then that various groups are not satisfied and are pressing for better financial terms. It is not easy to see where the extra money is to come from to meet these demands. Economy on non-essentials and making better use of the funds available suggest themselves as possible means of saving. Parliament keeps a check on government expenditure through various standing committees, and reports from such committees are coming to hand. Figures thus available show that the original estimates were very wide of the mark, and it may be noted that the medical statisticians were nearer the mark in their forecasts than those made by the Ministry; this point was stressed in a previous letter. Dentists, for example, have been found to be able and ready to work much more than the estimated 1500 chairside hours *per annum*. As a result dentists' earnings in many cases are higher than those of doctors, which is not felt to be right. In the year 1949-1950, 200,000,000 prescriptions were dispensed by chemists instead of the estimated 140,000,000. This notwithstanding, as is shown above, both dentists and chemists are not satisfied with their present rates of pay. Money spent on the ambulance services comes in for criticism by another parliamentary committee. The estimated cost for such services is £8,000,000 for the year 1950-1951, and the committee feels that improved control would lead to a substantial reduction in this sum. "Patients may choose to receive treatment at a hospital far away from their home and are entitled to free ambulance trans-

port, although the same treatment may be available at their local hospital." Also there seems to be little control over the mode of transport demanded by the patient. Thus an ambulance journey from North Wales to London costs £50, whereas the same journey for the patient and an attendant by train in a reserved compartment could have been made for £5 7s. 6d. Other similar cases of rising costs are quoted, and the committee feels that "unless the Ministry of Health take some action . . . there is a very real danger that, in the words of one witness, the day will come when all our vehicles are engaged on trivial work . . . and some desperately urgent case will die because it has had to wait to go into hospital". A number of useful recommendations to save money, and at the same time increase efficiency, are made in the committee's report. So the matter rests, and one's mind goes back to a famous test match at the Oval, where with fifteen runs wanted for victory, the last two men, both Yorkshiremen, were batting. They decided to make good the deficit by singles, stuck to their plan and won a great game. If the Minister had followed the example of George Hirst and Wilfred Rhodes and taken a small step at a time, he would have had by now a more efficient and contented health service.

"In Lighter Vein."

At a recent Burma reunion, Field-Marshal Sir William Slim told the following story. When he was driving himself one day on a bad road in Burma his car broke down, and he hailed a passing bulldozer, laden with odds and ends. On climbing in, he greeted the driver and said: "I am General Slim." The answer came pat: "Pleased to meet you, I am General Salvage."

Correspondence.

INTERNAL FIXATION FOR RECENT FRACTURES OF THE SHAFTS OF LONG BONES.

SIR: I was somewhat pained to find myself reported in your journal (July 29, 1950) as having advocated the use of internal fixation "in nearly every case of recent fracture" of long bones, in my remarks following Mr. Thomas King's paper on this subject at the Brisbane congress. I am troubling to correct this, as I feel that such misrepresentative reporting may tend to deter the more sensitive among us from making any comment at all at such gatherings, and also because I was attempting to draw attention to an aspect of fracture treatment which was ignored completely by the speaker in his spirited, if myopic, denunciation of treatment by internal fixation.

I referred to the risks attendant on the use of plaster of Paris splintage and the necessity of taking these risks into consideration in assessing the relative safety of various methods of treatment.

It is a painful truth that limbs cannot be immobilized for months on end without permanent and severe damage; a truth more evident to patients themselves, and to their insurance company's medical assessors, than to surgeons who judge the success of their treatment by signs of bony union on an X-ray film. Adhesions around muscles, tendons and joints, vasomotor and other circulatory changes, result in the cold, blue, painful stiff-jointed limb which is so commonly seen as an end result of prolonged splintage for fracture.

In those fractures, as of the femoral or humeral shaft and upper shaft of tibia, in which union can be expected in a comparatively short time (before immobilization has spoiled the soft tissues forever), I would be the last to deny that external splintage has a worthy place, but in deciding the fate of fractures in which accurate reduction and adequate internal fixation followed by early soft tissue mobilization is obviously necessary and desirable, I pray that he who starts back in horror from the dangers of operation, will not smile with time-honoured equanimity upon the permanent destruction of the beautiful muscle, tendon and joint mechanisms which may inevitably follow months in plaster.

And that was the point I had been attempting to make, sir. Let us, by all means, take heed of the dangers attendant on operative treatment of fractures and do not unwisely invoke them, but let our choice be made with due regard to the great, though less dramatic, dangers of prolonged immobilization.

Bones can be made to join after years of non-union with or without infection, but soft tissue spoliation is often painful, crippling and permanent. All this must be considered and weighed against the risks of operation so that fear and prejudice does not deny a patient the benefit of this where indicated.

All this I said and more, sir, when your reporter awoke to gather that I was advocating the use of "operative treatment of nearly every case of recent fracture".

I found it very vexing.

Yours, etc.,

JOHN WOODWARD.

12 Collins Street,
Melbourne, C.1,
August 21, 1950.

THE DISMISSAL OF DR. P. R. JAMES.

SIR: I wish to support the plea of Dr. E. P. Dark (August 26, 1950) that "our councils should be prepared to defend any doctor who is attacked because of his political beliefs".

No one in a democracy should suffer the ignominy of summary dismissal from his employment without an adequate explanation. The British Medical Association is powerful enough to press claims on the Government in other respects. What more pressing claim is there than the safeguarding of the rights of an individual medical man, the victim of what is, without further explanation, arrogant injustice?

Yours, etc.,

W. T. LESSLIE.

15 Hill Street,
Lithgow, 2W,
New South Wales.
August 28, 1950.

Congresses.

AUSTRALIAN AND NEW ZEALAND ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE.

THE Australian and New Zealand Association for the Advancement of Science will hold its twenty-eighth meeting in Brisbane from May 23 to 30, 1951. Dr. J. E. Caughey, of Auckland, is President of the Section of Medical Science and National Health, and a committee under the chairmanship of Dr. J. V. Duhig, Director of the Department of Pathology in the Brisbane General Hospital, with Dr. J. A. Inglis as secretary, has been formed to prepare the programme of the section. Anyone wishing to present a paper to the section or to suggest a topic for discussion should communicate with Dr. Inglis. Early enrolment for attendance is requested so that accommodation may be reserved. Information and enrolment forms may be obtained from Dr. J. A. Inglis, Medical School, Herston, Brisbane.

Post-Graduate Work.

THE POST-GRADUATE COMMITTEE IN MEDICINE IN THE UNIVERSITY OF SYDNEY.

Course in Advanced Medicine.

THE Post-Graduate Committee in Medicine in the University of Sydney announces that, as it is likely that the M.R.A.C.P. written examination will be held early in March, 1951, a course in advanced medicine suitable for candidates for this examination will be conducted for a period of twelve weeks beginning November 13, 1950. After a vacation of three weeks from December 18, the course will resume on January 8, 1951, and continue until February 23. Fees for attendance will be £31 10s., or £2 12s. 6d. per week. The programme has been arranged to take place exclusively in the afternoons, from approximately 2 p.m. to 5 p.m., on five days each week, and will include the following: didactic lectures on the more obscure aspects of internal medicine, designed to supplement the students' reading; lectures and tutorials in electrocardiography; ward rounds and demonstrations of cases at the principal metropolitan hospitals throughout the week; regular clinicopathological conferences; lecture-demonstrations in physiology and biochemistry, and discussions on applied physiology; lecture-demonstrations in pathology and hæmatology; demonstrations of the application of radiological methods of diagnosis to medical diseases and demonstrations of pædiatric and psychiatric cases.

The supervisor of the course will conduct tutorials on selected subjects, and students may discuss with him any problems arising in the course of their work. It is expected that candidates will devote considerable time to general reading, both of text-books and of current medical literature. The object of the course is to provide assistance and guidance for the serious students of internal medicine. It is desirable that candidates should have had considerable clinical experience in hospital and/or in medical practice before considering themselves prepared to take examinations for higher medical degrees or diplomas.

Fees are payable in advance at enrolment date, and early application is desirable. Applications to attend the whole or portion of the course should be in the hands of the Course Secretary, the Post-Graduate Committee in Medicine, 131 Macquarie Street, Sydney, not later than November 3. Telephones: BU 5238, BW 7483. Telegraphic address: "Postgrad Sydney."

POST-GRADUATE WEEK AT SAINT VINCENT'S HOSPITAL AND THE CHILDREN'S HOSPITAL, MELBOURNE.

A POST-GRADUATE WEEK will be held at Saint Vincent's Hospital and the Children's Hospital, Melbourne, from October 9 to 13, 1950. A series of lectures and demonstrations has been arranged by the members of the medical staff of these two hospitals. A printed programme is available. Inquiries regarding Saint Vincent's Hospital should be addressed to Dr. James F. Hughes, Clinical Secretary of Saint Vincent's Hospital, 33 Collins Street, Melbourne (telephone JM 1390), and those regarding the Children's Hospital to Dr. Mostyn Powell, 41 Spring Street, Melbourne (telephone JM 1757), or to Dr. Howard Williams, Children's Hospital, Carlton (telephone FJ 3171). Information is available also from the office of the Melbourne Permanent Post-Graduate Committee, 426 Albert Street, East Melbourne (telephone JM 1547).

Obituary.

ALFRED MEILLON LANGAN.

WE are indebted to Dr. C. H. Knott for the following appreciation of the late Dr. Alfred Meillon Langan.

Dr. Alfred Meillon Langan died in Cairns on July 20, 1950, at the age of fifty-seven years. He graduated at the University of Sydney in 1915, and served with the first Australian Imperial Force, being discharged with the rank of major. After the war he settled in Cairns in general practice, and he continued in this work until the time of his death. He served as part-time medical superintendent of the Cairns District Hospital from 1920 to 1937. He was responsible for much of the planning and expansion of the hospital during those years when Cairns grew in size from a small country town to its present-day size. He was always interested in local conditions, and published a paper in THE MEDICAL JOURNAL OF AUSTRALIA, August 3, 1935, in association with R. Y. Mathew on "The Establishment of 'Mossman', 'Coastal' and Other Previously Unclassified Fevers of North Queensland as Endemic Typhus". At his death, Dr. Langan had been president of the Cairns Local Association of the British Medical Association for several years. In this office he always showed qualities of wisdom, tact and good humour, which endeared him to his fellow practitioners. During the war years he was forced, because of the shortage of civilian doctors, to work very hard when his health was never particularly good, and this imposed a great strain on his constitution.

Dr. Langan took a most enthusiastic interest in the Cairns Golf Club, of which he was president for many years. He was a keen follower of many sports, and was at one time president of the Bowling Club and president of the Northern District Racing Association. From its inception, Dr. Langan took a keen interest in the Rotary Club of Cairns, and was greatly admired as an after-dinner speaker.

DISEASES NOTIFIED IN EACH STATE AND TERRITORY OF AUSTRALIA FOR THE WEEK ENDED AUGUST 26, 1950.[1]

Disease.	New South Wales.	Victoria.	Queensland.	South Australia.	Western Australia.	Tasmania.	Northern Territory.[2]	Australian Capital Territory.	Australia.[3]
Ankylostomiasis	*	..	1	..	..	..	..	..	1
Anthrax	*	..	..	..	..	..	..	..	..
Beriberi	*	*	*	*	*	*	..	*	..
Bilharziasis	*	..	..	..	..	..	..	..	..
Cerebro-spinal Meningitis	7(7)	2(2)	1	1	2(2)	..	..	..	13
Cholera	..	..	..	..	..	..	..	..	..
Coastal Fever(*a*)	*	*	*	*	*	*	*	*	..
Dengue	*	*	*	*	*	*	..	*	..
Diarrhœa (Infantile)	..	..	..	..	..	..	..	..	..
Diphtheria	5(3)	3(3)	4(4)	1(1)	6(6)	..	..	..	19
Dysentery (Amœbic)	*	..	..	..	..	..	..	..	..
Dysentery (Bacillary)	*	..	..	..	1(1)	..	..	1	2
Encephalitis Lethargica	..	..	..	..	..	..	..	..	..
Erysipelas	*	*	*	1	*	*	..	..	1
Filariasis	*	..	..	..	..	..	..	..	..
Helminthiasis	*	..	*	*	*	*	*	*	..
Hydatid	*	..	*	*	..	*	*	..	..
Influenza	*	*	*	..	*	*	..	*	..
Lead Poisoning	*	*	..	*	*	*	*	*	..
Leprosy	..	..	..	..	..	..	..	..	..
Malaria(*b*)	*	..	1(1)	..	..	..	..	..	1
Measles	*	*	*	193(152)	*	*	..	2	195
Plague	..	..	..	..	..	..	..	..	..
Poliomyelitis	10(6)	..	..	5(5)	2(1)	..	..	1	18
Psittacosis	*	..	*	..	*	*	*	*	..
Puerperal Fever	..	..	..	2(2)	..	..	..	..	2
Rubella(*c*)	*	*	..	*	..	*	..	..	..
Scarlet Fever	29(15)	14(11)	6(4)	9(6)	3(2)	6(2)	..	..	67
Smallpox	..	..	..	..	..	..	..	..	..
Tetanus	*	1	1	*	*	*	*	*	2
Trachoma	*	..	*	*	*	*	*	*	..
Tuberculosis(*d*)	36(17)	30(22)	23(17)	15(15)	21(15)	4(3)	..	..	129
Typhoid Fever(*e*)	..	..	1(1)	..	..	..	..	..	1
Typhus (Endemic)(*f*)	..	..	..	..	..	..	..	..	..
Undulant Fever	..	..	..	..	..	..	..	..	..
Weil's Disease(*g*)	*	*	19	*	*	*	*	*	19
Whooping Cough	*	*	*	6(2)	*	*	..	..	6
Yellow Fever	..	..	..	..	..	..	..	..	..

[1] The form of this table is taken from the *Official Year Book of the Commonwealth of Australia*, Number 37, 1946-1947. Figures in parentheses are those for the metropolitan area.
[2] Figures not available.
[3] Figures incomplete owing to absence of returns from the Northern Territory.
* Not notifiable.
(*a*) Includes Mossman and Sarina fevers. (*b*) Mainly relapses among servicemen infected overseas. (*c*) Notifiable disease in Queensland in females aged over fourteen years. (*d*) Includes all forms. (*e*) Includes enteric fever, paratyphoid fevers and other Salmonella infections. (*f*) Includes scrub, murine and tick typhus. (*g*) Includes leptospiroses, Weil's and para-Weil's disease.

His cheerfulness during the years of his illness and his devotion to duty in spite of it exemplified his wonderful spirit. His hypertensive patients could learn much from the example he set in the management of his own condition. The late Dr. Langan was charitable in the greatest sense of the word, and the community has lost a true friend as well as an able and well-loved citizen.

KEITH GADSDEN McCULLOUGH.

We regret to announce the death of Dr. Keith Gadsden McCullough, which occurred on August 24, 1950, at Kooyong, Victoria.

PATRICK JAMES KERWIN.

We regret to announce the death of Dr. Patrick James Kerwin, which occurred on September 4, 1950, at Brisbane.

Naval, Military and Air Force.

APPOINTMENTS.

The following appointments, promotions *et cetera* have been promulgated in the *Commonwealth of Australia Gazette*, Number 51, of August 31, 1950.

Royal Australian Air Force.

Citizen Air Force.

Dr. Douglas Wilson, M.B., B.S. (297509), is appointed to a commission with the temporary rank of Squadron Leader, 24th April, 1950, for part-time duties.

Dr. David John Howell, M.B., B.S., D.T.M. and H. (279950), is appointed to a commission, 17th September, 1949, with the rank of Flight Lieutenant.

The appointment of Flight Lieutenant A. S. Feddersen (257692) is terminated on demobilization, 31st May, 1950.

Active Citizen Air Force.

Flight Lieutenant W. A. Newnham (05978) is transferred to the Reserve, 18th July, 1950.

Air Force Reserve.

Percy Harris Cowen (033058) is reappointed to a commission with the temporary rank of Squadron Leader, 5th July, 1950.

Dr. Barry Francis Loughnan (257783) is appointed to a commission with the rank of Flight Lieutenant, 3rd July, 1950.

Corrigendum.

In the paper entitled "Seasonal Variations in Growth of the Composite or Mammoth Pre-School Child", by John Dale, published in the issue of August 19, 1950, at page 281, an error appears in Figure II. The curve at the top of the figure marked "3rd year of life" relates to the fifth year of life. The curve at the bottom of the figure marked "5th year of life" relates to the third year of life.

Nominations and Elections.

The undermentioned have applied for election as members of the New South Wales Branch of the British Medical Association:

O'Sullivan, Eibhlin Maire Eilis, M.B., B.S., 1950 (Univ. Sydney), 13 Black Street, Vaucluse.

Jacobi, Marian, registered in accordance with the provisions of Section 17 (1) (c) of the *Medical Practitioners Act*, 1938-1945, Mental Hospital, Orange, New South Wales.

Shand, William Neil, M.B., Ch.B., 1944 (Univ. Glasgow), 49 Church Street, Randwick.

Medical Appointments.

Colonel A. M. McIntosh, Dr. T. M. Furber, Dr. O. A. A. Diethelm and Dr. V. M. Coppleson have been appointed directors on the board of the Prince Henry Hospital, in pursuance of Section 6 of the *Prince Henry Hospital Act*, 1936, of New South Wales.

Dr. Peter Ronald Brett has been appointed Government Medical Officer at Dalby, Queensland.

Diary for the Month.

SEPT. 18.—Victorian Branch, B.M.A.: Finance, House and Library Subcommittee.
SEPT. 19.—New South Wales Branch, B.M.A.: Medical Politics Committee.
SEPT. 20.—Western Australian Branch, B.M.A.: General Meeting.
SEPT. 21.—New South Wales Branch, B.M.A.: Clinical Meeting.
SEPT. 21.—Victorian Branch, B.M.A.: Executive Meeting.
SEPT. 22.—Queensland Branch, B.M.A.: Council Meeting.
SEPT. 26.—New South Wales Branch, B.M.A.: Ethics Committee.
SEPT. 27.—Victorian Branch, B.M.A.: Council Meeting.

Medical Appointments: Important Notice.

MEDICAL PRACTITIONERS are requested not to apply for any appointment mentioned below without having first communicated with the Honorary Secretary of the Branch concerned, or with the Medical Secretary of the British Medical Association, Tavistock Square, London, W.C.1.

New South Wales Branch (Medical Secretary, 135 Macquarie Street, Sydney)—All contract practice appointments in New South Wales.

Victorian Branch (Honorary Secretary, Medical Society Hall, East Melbourne): Associated Medical Services Limited; all Institutes or Medical Dispensaries; Australian Prudential Association, Proprietary, Limited; Federal Mutual Medical Benefit Society; Mutual National Provident Club; National Provident Association; Hospital or other appointments outside Victoria.

Queensland Branch (Honorary Secretary, B.M.A. House, 225 Wickham Terrace, Brisbane, B17): Brisbane Associated Friendly Societies' Medical Institute; Bundaberg Medical Institute. Members accepting LODGE appointments and those desiring to accept appointments to any COUNTRY HOSPITAL or position outside Australia are advised, in their own interests, to submit a copy of their Agreement to the Council before signing.

South Australian Branch (Honorary Secretary, 178 North Terrace, Adelaide): All Lodge appointments in South Australia; all Contract Practice appointments in South Australia.

Western Australian Branch (Honorary Secretary, 205 Saint George's Terrace, Perth): Norseman Hospital; all Contract Practice appointments in Western Australia. All government appointments with the exception of those of the Department of Public Health.

Editorial Notices.

MANUSCRIPTS forwarded to the office of this journal cannot under any circumstances be returned. Original articles forwarded for publication are understood to be offered to THE MEDICAL JOURNAL OF AUSTRALIA alone, unless the contrary be stated.

All communications should be addressed to the Editor, THE MEDICAL JOURNAL OF AUSTRALIA, The Printing House, Seamer Street, Glebe, New South Wales. (Telephones: MW 2651-2.)

Members and subscribers are requested to notify the Manager, THE MEDICAL JOURNAL OF AUSTRALIA, Seamer Street, Glebe, New South Wales, without delay, of any irregularity in the delivery of this journal. The management cannot accept any responsibility or recognize any claim arising out of non-receipt of journals unless such notification is received within one month.

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